Lecture 19A • 11/14/11

Today we get to formally begin Sn1 and Sn2. Let's draw one example mechanism of the Sn2 reaction. I'll start out with a primary alkyl halide as my example. I'm going to go ahead and use a deuterated molecule, just so I could still have a primary group I'm using, but also have it be a stereocenter. We'll have an alkyl halide where we'll throw something like hydroxide at it. The hydroxide will attack the carbon with the bromine at the same time that bromine is kicked out, which will result in hydroxide substituting for the bromine; it also ends up causing an inversion of configuration. Let's discuss the six aspects of the reaction. What is the synthetic utility of this reaction? It's to convert an alkyl halide into a small number of other functional groups. Synthetic utility is we're going from an alkyl halide to an alcohol or an ether, or a thiol, or you're going to see a couple of other functional groups that this can be converted into. Primarily, we're going to see the formation of alcohols and ethers. What are the reagents? You need a basic nucleophile. We're going to talk about the difference between basicity and nucleophilicity. If you've got something that's a bit of both – basic means it likes to grab a proton; nucleophilic means it likes to seek out positive charge – those are the types of reagents that will work. For example, you've seen sodium hydroxide, but you could have the anion of an alcohol, a deprotonated alcohol, in general called an alkoxide, this one specifically called ethoxide. You can have sodium cyanide – this is going to be one of those other products. When you put a –CN on a molecule, it's a functional group called a nitrile. The reagents are all negatively charged; the sodium's just the counterion; it's a negatively charged species. They're all, to varying degrees, basic; methoxide, very similar to hydroxide, about the same level of basicity. Cyanide ion not as basic, but still a negative charge. Because they're all negatively charged, they're all nucleophilic, they want to seek out that relatively positively charged carbon center. Cyanide is one of the smaller number of reagents where the carbon itself ends up being the business end of the attack, but most of the nucleophiles that we'll encounter are organic. [halides not organic and not basic]

What about conditions? Generally this reaction works best if you use a polar aprotic solvent. The mechanism, we already have above. Something that I could say about the mechanism is that it is anionic and concerted. It is the negative charge that causes this reaction to occur, and it all happens in one step. What about stereochemistry? We have inversion of configuration; the stereocenter inverts. As far as regiochemistry, it is specific – it is at the position of this thing called the leaving group. In this case, it's where the bromine is located that the attack occurs. In general, whatever gets kicked off, that's the leaving group, that's the position that the reaction occurs at. [road map for lecture] We have four items that we need to discuss – the substrate, the main thing being attacked; the nucleophile used in the reaction; the leaving group that gets kicked off in the reaction; and how does solvent affect it.

Let's review these six things one last time. What do the terms nucleophile and electrophile mean? A nucleophile wants positively charged; a nucleus is positively charged. Something that's negatively charged makes a good nucleophile. What's an electrophile then? Wants electrons, wants negative charge, so usually something that's positively charged is going to be a good electrophile. In this particular reaction, to dissect it a little bit, the hydroxide is going to be the nucleophile, because it seeks positive charge. This molecule that's being attacked, I'm going to call it the substrate. We can think of it as the target of this reaction. The bromide, in this case, is what is known as the leaving group. It is the thing that gets kicked out during the reaction. Why is it that this nucleophile is able to attack? Because we have some kind of relatively positively charged center. Alkyl halide are far more reactive than alkanes because there is this polarity. In fact, there'll be almost no reaction of alkanes that you'll learn because they're generally just not reactive; there's not good place for a molecule to grab on to. This nucleophilic substitution happens because you've got this little polar place on the molecule for a nucleophile to be able to attack.

In terms of mechanism, this mechanism is concerted; that's why this reaction ends up occurring with inversion of stereochemistry. Many text go on a long story that: when this substitution occurs, could it be random how the group ends up on there; is there an explanation for that? Or could it be that the groups comes off and then the attacking group comes in from the front side where that leaving group had been. Then the story winds around eventually to: what really ends up happening is this thing called inversion; one of the earliest cases was called the Walden inversion, after the gentleman who discovered it. In that case, it was thought that the attacking group was coming from the back side of where the leaving group is, pushing that leaving group out. What is the explanation for why that occurs? Let me try to draw something. If you think about sigma bonds and sigma star bonds, the sigma bond would exist between the carbon and bromine atoms; the sigma star bond has orbitals that point to the outside of the nuclei. If you remember our discussion of why a bond is favorable and an antibond is unfavorable, the bond if favorable because electrons do end up between nuclei; the antibond is unfavorable because the electrons end up on the outside of the nuclei that exposes the two nuclei to each other. Exactly opposite in direction of where the bromine is pointing, opposite that the sigma antibond is pointing. That's the orbital that electrons are adding into once the nucleophile comes in to attack. If we had hydroxide that was approaching, those electrons go into that antibonding orbital. Once they do, they cause the carbon-bromine bond to break, because you just filled up the antibond. But because it broke and we've got these new electrons coming in, a new bond forms, but it forms in the opposite direction of the old one. That's why inversion of configuration occurs. In an Sn2 reaction, the nucleophile attacks by adding into the sigma start bond to the leaving groups. You might think: there's another sigma start orbital on the other side of bromine, why doesn't it attack there? Because bromine's more negative, and if this is a nucleophile that wants positive charge, it's going to want to attack the carbon side, because it's got the relative positive charge.

So the nucleophile attacks into the sigma star bond. Since electrons are added into the antibonding orbital, the bond with the leaving group breaks. This allows a new bond to the nucleophile to form, but in the exact opposite direction that the bond had originally been pointing. Because it's exactly opposite in direction, that's why that leads to this inversion of configuration. This is to tie mechanism to stereochemistry – the idea being that first thing that you need to learn in any reaction is the mechanism, since you're going to use that to argue why does the stereochemistry do something special or not do something special; why do you end up with multiple products or not multiple products.

In this case, because this is a one-step reaction, we could write a reaction coordinate diagram that looks like this. If we assumed that this is an exothermic process, which most substitution reactions are going to be, then we'll have one transition state between the reactants and products, but there won't be a dip in this diagram; the [intermediate] is not isolatable. When I say isolatable, I should say identifiable, because intermediates you often can't trap and pull out of reaction mixture, but you can spot them or there's evidence for them. This would just be a transition state, at some point along the process where bonds are stretching and starting, bonds are starting to form, but neither's quite finished yet. The intermediate would look like a drop-off point; the energy would dip for a moment; and all of the bonds that are going to break are broken, all of the bonds that are going to form have formed, so you're not in between a reaction step. You finished a reaction step, but maybe you didn't get to the product. That's an important difference. Sn2 reactions are going to look like this: one step only.

What I would to like to introduce is the idea of predicting the structure of the transition state. Remember that you learned something called the Hammond postulate. In this case, the transition state lies closer to reactants. What does the Hammond postulate say? The structure of the transition state [not the intermediate] matches more closely whatever's closest in energy to it, whether it's the product, the reactant, or an intermediate. Whatever's on either side of the transition state, whatever's closer in energy, that's more what the transition state looks like. What's the transition state going to look more like in this case? It's going to look kinda like the reactant. The bond's going to start to break, another bond's going to start to form, but it's going to be kinda skewed towards the bond still being there. If we wanted to try to draw the structure of the transition state, I might do something like this. I'll start out with the bromine pointed to the, pointed out towards us. I'll just say bromine's on my right, I've got hydrogen on my left; the deuterium is pointed away from me, and then I've got this alkyl group that's pointed towards me. Imagine that I'm looking along the molecule but the main part of the molecule is in line with my eyesight. If I'm looking down the alkyl group and a hydrogen I see bromine on one side, deuterium on the other. As the hydroxide comes in to attack, the transition state would look something like this. The bromine bond is starting to break; the hydroxide bond is starting to form. They hydrogen is now pushed to being in the same plane as the deuterium and as the alkyl group. Recognize that this is unusual, because I'm writing two things with wedges; up to this point I've been saying that any time you write a stereocenter, you have to have a wedge and a dash. But this is not a normal stereocenter; this is not a normal carbon, because I'm trying to show five things bound at the same time. In fact, if ignored the difference between all the different substituents, what geometry would this transition state have? Trigonal bipyramidal. In other words, these three things form a triangle, and the bromine and hydroxide are pointed opposite directions from the face of that triangle. Another way to think about it is: what if you had the umbrella idea, where you have bromine at one end and the other three substituents pointed away from bromine. In a strong wind, that umbrella inverts; bromine's leaving and the handle is now the hydroxide. Coming out of this transition state, what we have is now hydrogen's been pushed to the other side of the molecule; hydroxide that just came in is on the left, the opposite way. We still have the deuterium and the rest of the molecule, the alkyl portion of it, pointed the same way as it was originally.

I've drawn the transition state; I'm going to show you other transition states in the future. But if I'm asking for a mechanism, I say don't show transition states – partly because it can be difficult to draw like this, and partly because they're not isolated intermediates; we don't care, in certain way, what the transition states look like. We've gone through the exercise once. It's important because it's related to this inversion of configuration. But in the future, if I ask what's the mechanism, you draw something just like this; you wouldn't show that transition state.

If you form a carbocation, normally you can't take a carbocation and put it in a bottle, but you could detect it and you could trap it and indirectly prove that it formed. Or, spectroscopy is getting good enough, you can actually monitor that bond-breaking event.

Let's move to factors that affect an Sn2 reaction. [commentary on when kinetics were introduced] Let's focus now on substrate. If I compare methyl bromide versus ethyl bromide versus isoproyl bromide versus t-butyl bromide, if you look at the relative rates of reaction.... In this case, saying something occurs more rapidly, we're going to make a connection between that and what's going on energetically. If the relative rate of a secondary alkyl reacting is about one, a tertiary is zero, meaning unreactive; versus a round figure of 40 for a small primary alkyl halide, versus about 200 for the methyl group. What is the reason that there's this huge spread of reactivity, this difference of reactivity between the different kinds of substrates? Steric hinderance. Since the Sn2 reaction depends on the nucleophile attacking directly the carbon bearing the leaving group, steric hinderance around that position will slow the rate of reaction. This can occur even if not right next to the leaving group you've got steric hinderance. For example, neopentyl bromide is this substrate where you have five carbons that form a cross pattern. If you react it with sodium hydroxide, there is [effectively] no reaction.

Why? Because even though it's a primary alkyl halide, you've got this set of three methyl groups that are also in that area, they're also causing steric hinderance. There's enough steric hinderance even being a position away like this that it still causes the bromine to be blocked.

What about a few other interesting cases, though. Do you think this should be a molecule that should react? The answer is no; why do you think that might be? What would be the direction of attack? It has to be exactly opposite from where the bromine's located, and if this molecule is planar – which it is, cause everything is sp2-hybridized – that would mean that the nucleophile would have to attack straight through the molecule to get to the bromine. There's simply too much steric hinderance for any kind of attack to occur. Phenyl is a common name for benzene when benzene's the substituent. Phenyl halides do not undergo Sn2 because of too much steric hinderance; attack would have to occur through the ring. More steric hinderance, less reaction because the nucleophile just can't get there.

Let's get to the nucleophile. Let's talk about nucleophilicity – it means the desire of a negative charge to seek out a positive charge, how strongly does a compound seek positive charge. We can stop right here and compare two different nucleophile: water versus hydroxide. They both have oxygens; those oxygens are going to have lone electrons. Which of these two do you think is more nucleophilic? Hydroxide. Why? Because it's got the negative charge. If nucleophilicity is about wanting to seek positive charge, things with negative charges are going to be lots more nucleophilic than the equivalent structure that doesn't have a charge. Hydroxide is much more nucleophilic because it has a full charge on it. What about basicity, which is how able is a compound to remove an H+ from something. If you've got electron withdrawing groups near a hydrogen, if you have the ability to form resonance after the hydrogen is removed, then these are things that are going to make that hydrogen more acidic; turn that back around, things that are more acidic mean their conjugate bases aren't as strong. Some good strong bases are things like, in general, deprotonated alcohols; this kind of ion is called an alkoxide, which is kinda like take alkyl and combining it with the word oxide.

Let me show you a case where there's a difference between nucleophilicity and basicity. Let's compare hydroxide versus the sulfur equivalent. Water, it's pKa is 15.74; hydrogen sulfide, it's going to have a pKa of 7. Which is the stronger base, hydroxide or SH-? Hydroxide. But, the SH- is the stronger nucleophile. If you put both SH- and OH- in the same reaction flask, and then threw an alkyl halide at it, it's going to be the sulfur that reacts with it much more quickly, even though the hydroxide's the stronger base. What's the difference between oxygen and sulfur? Sulfur's lower in the periodic table, so it's bigger and squishier. If you have sulfur coming in to attack this antibonding orbital and start to give it electron density, that process of giving some electron density to the orbital happens more easily with sulfur because sulfur is not as small and tight an ion. There's this term polarizability, which means able to become polarized. Larger ions, one's that are physically larger, as squishier, you could say, which means that the electron density can be displaced – or polarized – more easily. Since sulfur is more polarizable than oxygen, it can initiate the bond formation more easily than oxygen can – more easily, less energetically unfavorable to do so means a faster process. Therefore, sulfur, in the equivalent kind of molecule, makes a better nucleophile than oxygen. Since sulfur is more polarizable than oxygen, the process of forming a bond occurs more easily, and therefore more quickly, for sulfur versus oxygen – which means sulfur is the better nucleophile than oxygen in similar molecule. Of course, we could probably find some random case where the oxygen's better; we're comparing two almost identical structures, only difference being oxygen versus sulfur. More electron density starts pouring into that new orbital. Oxygen's got a tight hold on its electrons; those electrons will done, but the process of starting that bond formation is a little tougher because oxygen's holding so tightly onto its electrons; they're not as polarizable. It turns out that that polarizability has a huge effect, even though it's not as basic.

Why does basicity matter? Because if you end up with a molecule like this, where you have a tertiary alkyl halide, and if you have a very basic nucleophile – especially something that is a very sterically hindered nucleophile its own self, so it makes it hard for that oxygen to get in to attack something – then it becomes a little easier to pull of a hydrogen, then, instead of trying to do an actual substitution. If you pull off that hydrogen, the pair of electrons that's in that hydrogen can swing around and kick off that leaving group, which means you end up forming an alkene. This is an elimination reaction – specifically, an E2. We want good nucleophiles, but we have to worry about whether something is basic because we have to worry about side reaction, unwanted reactions that you get when the nucleophile is too basic.

To summarize, in Sn2 reactions, they require strong nucleophiles, which are generally basic. It needs something able to attack. These nucleophiles are often, but not always, basic. Extremely basic or sterically hindered nucleophiles can undergo elimination instead of substitution.

The leaving group. The structure of the leaving group can have a huge influence on the reaction. What makes a good leaving group? Good leaving groups are the conjugate bases of very strong acids. Why should that make sense? If you're trying to get a pair of electrons to leave, if that pair of electrons wants to go right back and attack something, why would that group come off in the first place. I made this distinction between nucleophile and base, but it turns out that, for the leaving group, base strength is related to how likely it is to come off to the molecule. For example, let's say that I had a halide. Although halogens are leaving groups, they're also nucleophiles. Look what would happen if I tried to take a bromide and kick off hydroxide. I'd make my alkyl bromide, but I'm kicking hydroxide off in the process.

Hydroxide is a strong base, a strong nucleophile, it would turn right back around and kick the bromine back off. More generally than this, if you tried to take an alkane and take even hydroxide and push off that hydrogen, you'd form an alcohol, but you'd form H-, which is really basic, so that reaction also would not want to happen.

What are some good leaving groups, then? What are some species that have strong conjugate acids. Halogens, but not all of them – fluoride is not a good leaving group at all. Why? Because it's basic, because HF is a weak acid. Chloride, bromide, iodide, they're all from strong acids; in fact, HI is stronger than Br is stronger than Cl. Generally, if you can get away with it, if they're available, alkyl iodides are sometimes preferred. There's one more type of group I'll introduce. There's a group of molecules called sulfonates that have this structure: some kind of alkyl group attached to what otherwise would look like sulfuric acid. In fact, if you put a hydrogen on there, made an acid, it is a strong acid, because it is so structurally similar to sulfuric acid – maybe not quite as strong an acid, but still very strong. These sulfonates also make really good leaving groups. Later on we're going to learn how to take an alcohol – a molecular that is not a leaving group – we'll learn how to change the alcohol into a sulfonate, which means it now is a leaving group, which now means we could make the molecule undergo some kind of reaction.

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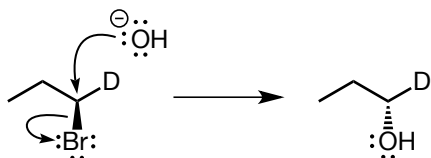6) regiochemistry : specific (@ leaving group)

In Sn2 rxn, the nucleophile attacks by adding into the sigma start bond to 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 –> inversion of configuration
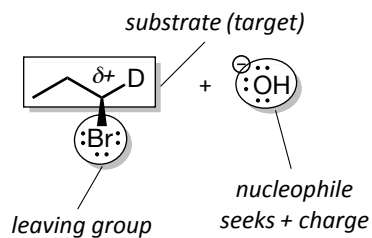
Factors that affect an Sn2 rxn

1) Substrates – SInce the Sn2 rxn depends on the nucleophile attacking direct[ly] the carbon bearing the leaving group, since steric hinderance around that position will slow the rate of reaction.
phenyl halides do not undergo Sn2 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)
Sn2 rnxs require strong nucleophiles (needs something able to attack), which are often, but not always, basic. *Extremely basic or hindered nucleophiles can undergo elimination instead of substitution.

3) leaving group – good leaving groups are the conjugate bases of very strong acids.
Examples: Cl-, Br-, I- (not F-); I- usually better than Cl- since HI is a stronger acid than HCl
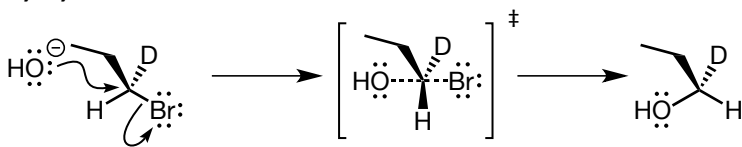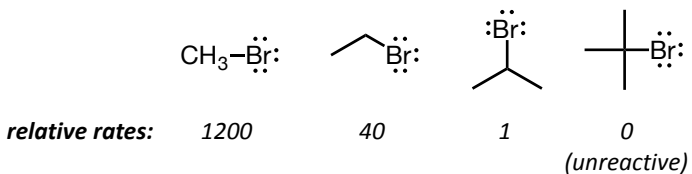sulfonate – strongly resembles sulfuric acid

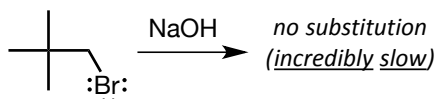**Structures**

11/14/11 lec • 1

11/14/11 lec • 2

substrate (target)

leaving group

*nucleophile
seeks + charge*

11/14/11 lec • 3

11/14/11 lec • 4

$$CH_3-\ddot{B}\ddot{r}: \qquad \overset{\ddot{B}\ddot{r}:}{\diagup} \qquad \overset{:\ddot{B}\ddot{r}:}{\diagup} \qquad \overset{:\ddot{B}\ddot{r}:}{\diagup}$$

relative rates: 1200   40   1   0
                                                    (unreactive)

11/14/11 lec • 5

NaOH

*no substitution
(incredibly slow)*

11/14/11 lec • 6

Nu:

11/14/11 lec • 7

elimination (E2)

11/14/11 lec • 8

11/14/11 lec • 9

sulfonate