

Lecture 20B • 11/17/11

[substrates][nucleophiles]

Leaving groups – A good leaving group is usually the conjugate base of a really, really strong acid. What's the logic behind this? If you want to push something off of the molecule, you want something that can easily be dissociated. Although it's not hydrogen that these leaving groups are originally connected to, kinda the same reason why a hydrogen would want to dissociate from something is the same reason why an anion might want to come off of a carbon chain, because if it's a pretty stable ion, if that negative charge is well-tolerated or well-distributed on that ion, then it's easy to form. Things like chloride, bromide, iodide, the types of things that are readily formed, at least in aqueous solutions, those three ions specifically make really good groups. Fluoride, however, although it's a halogen, is a very poor leaving group. Why? Because hydrofluoric acid, although a very hazardous compound, is a weak acid, which means it doesn't really dissociate all that much. If you tried to do an S_N2 reaction with an alkyl halide, as long as it's chlorine, bromine, or iodine, the reaction works really well. In fact, iodide ends up being the best leaving group of those four halogens. Why do you think that might be? The HF bond is [stronger] than the HCl bond is [stronger] than the HBr bond is [stronger] than the HI bond, because of the poorer orbital overlap. You've got iodine, which is a big, squishy ion, with hydrogen that's bonding with it; poor overlap means a weaker bond. HI, hydroiodic acid, is the strongest of the four acids, then hydrogen bromide, hydrogen chloride; hydrogen fluoride is a weak acid. HI, HBr, HCl, those are in order of decreasing strength, but they all three are still strong acids. HF is a weak acid. If we look at leaving group ability and compare I^- , Br^- , Cl^- , F^- , it increases in exactly the same direction, except that fluoride is not a leaving group. Why not? Because it [fluorine]'s basic, and because fluorine makes really good bonds with carbon, it really doesn't want to be displaced.

There's some other really good leaving groups. I want to show you one class of compounds that we're going to very commonly encounter. This is a notation that you might not have seen before, where I use R and R'. The prime is just to show that it's different or possibly different from R. There's two different alkyl groups; maybe they're the same, but possibly not. This kind of structure, where you have the sulfur with three oxygens that's trapped in between these two alkyl groups, this is called an alkyl sulfonate. If we compare this structure to sulfuric acid, we'll see there's a fair bit of similarity. Why is sulfuric acid so acidic? The sulfur is pretty darn δ^+ because of all the oxygens that are around it, and electron density can be pulled to the sulfur therefore, and, if you had dissociation of one of the two hydrogens, you're going to end up with an ion that has extensive resonance stabilization of that negative charge. You might recall that we discussed three different influences on a molecule that causes it to be more acidic. One of them was resonance stabilization itself – that if you form something that has resonance stabilization that makes it easier to form. If we're talking about acids dissociating, means we're going to end up with a stronger acid. What were the other two factors that could affect acidity? Inductive effect – which means that you're going to have something electronegative pulling electron density towards it. What was the third one? Hybridization – if you have an sp^3 carbon versus sp^2 versus sp , the sp carbon was the more acidic one. In a similar fashion, it is very easy, comparatively, for the sulfonate group to dissociate. Sulfonates are good leaving groups because they're easily dissociable.

Why, this random group sulfonate, should we care about? Because you can easily convert an alcohol into one of these sulfonates. For example, keeping it as a generalized reaction, start with an alcohol and react it with a version of the molecule that has a chlorine there instead. This is not an S_N1 or S_N2 reaction, but let's use some of what we've learned from this to rationalize what might happen here. We have a sulfur that's very δ^+ ; it's got two oxygens and now this chlorine that are around it; that chloride, itself, would be able to easily dissociate from sulfur, because the chloride ion is a favorable ion. What can happen is the alcohol attacks that sulfur center. It allows us to take an alcohol and turn it into one these alkyl sulfonates. Why is that important? Because an alcohol is not a leaving group. Just to have written an example of this down – even if we have a good nucleophile, like the SH^- ion, you will not get a successful reaction at all, if you're trying to displace something like hydroxide. Hydroxide, remember, is a poorer nucleophile. In terms of basicity, it would be terrible to try to make hydroxide dissociate. When you put an $-OH$ group on a carbon, it's no longer an ionic group, because carbon-carbon single bond, although polar, is still a covalent bond. But alcohols are very, very, very common synthetic utilities [story of alcohols and o-chem] You can convert nearly every functional group into an alcohol, and an alcohol into nearly any other functional group – sometimes just in one reaction, or just in a small number of reactions. This is an example here.

I can take an alcohol that [doesn't] have a leaving group, just hit it with this compound, and then end up with an alkyl sulfonate, which now has a leaving group. Let me show you two specific sulfonates. When you have a benzene ring with just a methyl group on it, that is toluene. If you substituted at the other end of it, then we're going to have para-toluene. This is a para-toluenesulfonate. For short, it's called a tosylate. Tosyl chloride, you can react with an alcohol, is a very inexpensive, easily obtained solid (so it's easily manipulable, very easy reaction, very easy to form tosylates that end up being really good leaving groups. Besides the fact that it's a leaving group, because this is a conjugate base of a really strong acid, that means that this tosylate ion when it dissociates, is not at all nucleophilic, so it'll leave and it'll just sit there. Very similar structure is if we just had a methyl group on there. That starting material's a liquid (which is not necessarily a bad thing). This is an alkylmethanesulfonate. The short name for this is mesylate. Both these groups, because they're so common, have abbreviations that you can use. These abbreviations don't include the oxygens that are connected to the alkyl group.

Tosylate is abbreviated Ts, and mesylate Ms. I'm using methanol, ethanol, propanol, and butanol as my example molecule. The alkyl portions of those can be abbreviated as Me, Et, Pr, and Bu. The abbreviations for propyl and butyl are not as common, but you will see them. Methanol and ethanol frequently abbreviated this way.

4) Solvent

An S_N2 reaction is more favorable if you use what's known as a polar aprotic solvent. The polar aspect of that, you could make an argument using reaction coordinate diagrams. I want to focus on the aprotic part of it. S_N2 reactions occur more rapidly in polar aprotic solvents. Aprotic solvents are solvents that do not have easily dissociable protons, nor do they have protons that easily undergo hydrogen bonding. If I say that they don't have easily dissociable protons, that means they're not acidic; we'll say pK_a s significantly greater than that of water. Water has a pK_a of 15.74, so we'll say significantly greater than 16 and do not have protons that easily hydrogen bond. Why does something being aprotic matter for an S_N2 reaction? Think about the mechanism for the reaction. You've got this nucleophile that's gotta charge its way through solution to attack the substrate. If the nucleophile ends up spending a lot of time with the solvent, then effectively, that's going to slow down or block its approach to the substrate. In fact, for one set of nucleophiles, it can cause a difference in the nucleophiles' reactivity. What I'm referring to, specifically, are the halogens. Let's say that we had an ideal solvent where the solvent didn't interact at all with halogens. Out of fluorine, chlorine, bromine, or iodine, which of those ions would you expect would be the better nucleophile? Iodine? Why might you say iodine? HI is a strong acid, but that makes iodide a better leaving group; at the moment I'm asking about it being a nucleophile. Polarizability? No. That might be the argument we could make; we did talk about oxygen versus sulfur, that even though a nucleophile with sulfur's less basic, because of its increased polarizability, it ended up being the better nucleophile. That doesn't end up being the case with the halogens.

In the halogens' case, the basicity factor ends up being more predominant – at least if you are in an aprotic solution. But if you're in a protic solution, where these halides could interact with the solvents, fluoride, being a tiny, small ion, gets easily surrounded by a solvent; the solvent can form what's called a solvent cage. If fluoride is blocked from moving as well because it's interacting with the solvent, then it becomes a poorer nucleophile. Iodine, being big and squishy, it's hard for it to become trapped in the solvent; it moves more easily through solution, and so it becomes, relatively, the better nucleophile. Any of those interactions in a protic solvent would be slower, but fluoride is slowed down the most. In an aprotic environment, in which the nucleophile does not significantly interact with the solvent, fluoride is the most nucleophilic of the halogens due to its basicity, which outweighs the polarizability of iodide. In protic solvents, however, the solvent more greatly interacts [with] or traps the fluoride, decreases its reactivity, which effectively makes it a poorer nucleophile compared to the other halogens. To put a picture on it, imagine a smaller fluoride ion and a larger iodide ion. If you were in something particularly protic, like water, we know that the hydrogens of water are delta positive, so fluoride is easily surrounded by water. Iodide gets surrounded by water, but can't be as tightly held cause it's such a big ion. If we drew the four halogens side-by-side, we could say in the aprotic solvents, fluoride is more reactive; iodide is more reactive in protic solvents.

Let's see some common examples of polar aprotic solvents. One is dimethylsulfoxide, which is most commonly referred to by its abbreviation DMSO. DMSO is a sulfur analog of acetone. Note the lone pair on the sulfur; that's very, very commonly missed. The other common solvent, its full name is N,N-dimethylformamide. Formaldehyde is a one-carbon aldehyde; it just has a carbonyl bond with hydrogens on carbon. Formamide is where you have that carbonyl attached to a nitrogen instead of a hydrogen; formamide is a one-carbon compound. Formaldehyde comes from the word formica which is Latin for ant; formic acid happens to be part of the component of the sting of an ant bite, certain kinds of ants, at least. N,N-dimethyl: the N refers to the fact that we have substitution on the nitrogen and not on the carbon. The compound structure is this; it also more commonly goes by its abbreviation of DMF.

We made our first pass through S_N2 ; let's start working on S_N1 . For the S_N1 reaction, I'm going to use a tertiary substrate. In an S_N1 reaction, a tertiary substrate ends up being best because tertiary carbocations are more favorable to be formed than secondary and primary and far, far, far better than a methyl. First thing that's going to happen reaction-wise is this dissociation. I'm using a mesylate as my example leaving group. Although it is ionic, because it is not basic, you could technically have a halide be the nucleophile at this point. The only reason I'm using this as an example is because not all S_N1 reactions are composed of three steps. Every other time I've shown you S_N1 , I've done it with water or an alcohol being as the nucleophile; because of that, once that oxygen attacks in, you have an extra step afterwards where the hydrogen dissociates. If the nucleophile itself happens to be negative, which occasionally can happen for S_N1 , you're only going to have two steps in that reaction. If we're trying to more formally cover the reaction, I want to make sure that I've shown you that this is the minimum number of steps involved. Iodide would attack, and we'd end up with an alkyl iodide as our product. As we did for the S_N2 reaction, let's draw up a reaction coordinate diagram and posit some transition state structures for this reaction.

Let's presume that this reaction is exothermic; generally, for a successful substitution reaction that's gotta be true. We're gonna form a carbocation as an intermediate. Because we're dissociating, that means that that carbocation's going to be higher in energy than the reactant. From previous discussions, we might remember that the first step in this process, the formation of the carbocation, is the more difficult step of the reaction, which means when I'm drawing the curve, I better make sure that the activation barrier for the first step is larger than the activation barrier for the second step.

I'll have my reactants, my intermediates, and my product, and I'll have two different transition states. Recall the Hammond postulate says that whatever the transition state is closer to in terms of energy, the transition state therefore matches structure-wise whatever is closest to it in energy. Both of the transition states, in this case, are closer to the carbocation, so both of the transition states are going to look more like a carbocation. It's kinda boring, in this case, to draw the two transition states because, for transition state one, all that's happening is a bond is breaking; notice I used the Ms abbreviation for mesylate here. For transition state two, all that's happening is a bond is forming; we could draw a dotted line like this. But at least we've gone through the process of trying to identify these transition states.

Now, the six aspects of the reaction: utility, reactants, conditions, mechanism, stereochemistry, regiochemistry. First, the utility. It's still similar to an Sn2 reaction. Why do we have two of these reaction mechanisms then? Because primaries can't do Sn1; tertiaries can't do Sn2; so there are two different reaction pathways if you want to do substitution. I'm still going to refer to alkyl halides being my main starting material, but realize that I've just shown you these sulfonates that could be starting materials as well, so don't forget about those. More commonly, you'll see examples with alkyl halides. You can convert alkyl halides to the same kind of groups you could for an Sn2 reaction – alcohols, ethers, and thiols. In terms of reagents, you usually need weak, non-basic nucleophiles – emphasis on the non-basic. If you've got a really basic nucleophile, it would try to do substitution if it could, but in Sn2 style; or, remember we talked about this side reaction that could occur, the elimination reaction. You need something not basic and preferably something not terribly nucleophilic; if it was, it'd try to do an Sn2 reaction. What about solvents? It's protic solvents; protic solvents generally polar solvents. The nucleophile itself is often used as the solvent in a [n sn1] reaction. Mechanism, we have above here; we could say that it's cationic and stepwise (those two are usually associated with each other). Stereochemistry – we have loss of configuration. Regiochemistry – not always highlighted in this reaction, but since this is a cationic intermediate, quite technically you could have carbocation rearrangement – possibility of carbocation rearrangement. I say possibility because it doesn't always happen. For example, the reaction up top here – you form that tertiary carbocation, in terms of energy, no way will it want to make a primary carbocation. Sure, there might be a one-in-a-zillion chance that just the right set of coincidences occur that one molecule or so of the primary product ends up forming, but not really likely.

Let's go over the stereochemistry aspect and review that. I'll use a chiral starting material. I'll make a tertiary alkyl halide. That's going to dissociate as the first step of the reaction. We'll make an intermediate. What is the geometry or the hybridization of that carbocation we just formed? It's sp², and therefore it is, in terms of shape, plane. Since it's planar, all other factors being aside, the carbocation can be attacked in principle from either up top or below. If there were no other factors, since this is planar, it should really be an equal probability that it will be attacked from above and below. If that happens, you get two products, you get them in equal proportion. Since you did start with just one stereocenter, but it become equally scrambled, you end up with a racemic mixture, where you have a 50/50 mix of the two enantiomers. Let me point out here that this is sp²-hybridized and it is planar. Since the geometry of the carbocation is planar, attack by the nucleophile could occur from either side, producing two products. To make a complete example, let's say that I had that same alkyl halide that I threw ethanol at. We're going to end up with two ethers. If both products form in equal proportion, that means we're going to end up with a racemic mixture. But, let's say for the moment, that in this cyclic compound I just drew, the methyl group next to – not on the same carbon as – next to the leaving group, let's pretend it did not have any kind of steric effect on this molecule. If, therefore, this reaction occurred with 50/50 proportion of forming the two different products, would that reaction mixture be racemic. No; why not? The problem is you have two stereocenters. Even though one of them might end up being scrambled, the other one does not. You have a 50/50 mixture of diastereomers; that would not be racemic, so you would still have an optically active solution, even if you had a 50/50 mix of both products. Just because you make two products doesn't mean you make a racemic mixture; it's only if you make just enantiomers that form in equal proportion do you end up with a racemic mixture. Since I used just one stereocenter, in this case, if both products form in equal proportion, a racemic mixture will result.

But, even if you do have something where you really do have a planar intermediate, and there really is no other group near it that's causing some kind of steric hinderance, you still might not end up with a racemic mixture because of what's called an ion pair. In solution, even after dissociation, you might have the pair of ions trapped in a common solvent cage. The ions have separated from each other, but they've not fully, physically moved apart from each other. Imagine if we had a situation like this, where we have the carbocation being planar; we formed a p orbital because of dissociation, but if bromide was our leaving group, what if the bromide is hanging out on one side versus the other of the molecule? Bromide can only dissociate one way; it can't tunnel through the molecule and come out the other side, so when the bond dissociates, it only ends up on one side specifically. If that remains trapped in the solvent cage, it doesn't move away, attack from the other side's gonna end up being more likely, even though you have a planar intermediate. These solvent cage effects can sometimes be great, sometimes be not. You might have reactions that end up with racemic mixtures, but it's common the case that you don't because of this effect. If both products were formed in equal proportion, you would have a racemic mixture; however, after dissociation, ions can be trapped as an ion pair in a solvent cage – solvent cage meaning the solvent is surrounding and preventing, to some extent, the ions to move. This is not a true bars and chains type of cage; of course, as everything is sloshing around in solution, eventually the molecules can move out of that cage, but if it doesn't happen quickly enough, by the time the nucleophile comes in to attack, you could have preferential attack at one side of this carbocation. An ion pair can lead to a nucleophile preferentially attacking one side of a carbocation versus another.

3) Leaving groups – Good leaving groups are the conjugate bases of strong acids. Sulfonates make good leaving groups because they are easily dissociable.

4) Solvent – S_N2 rxns occur more rapidly in polar aprotic solvents.

Aprotic solvents are solvents that do not have easily removable protons (weak acids, $pK_a \gg 16$) and do not have protons that easily hydrogen bond. In an aprotic environment – in which the nucleophile does not significantly interact with the solvent – fluoride is the most nucleophilic of the halides, due to its basicity (which outweighs the polarizability of iodide). In protic solvents, the fluoride ion more extensively interacts with (or is “trapped” by) the solvent, so it becomes the poorer nucleophile. Example polar aprotic solvents: dimethylsulfoxide (DMSO); N,N-dimethylformamide (DMF)

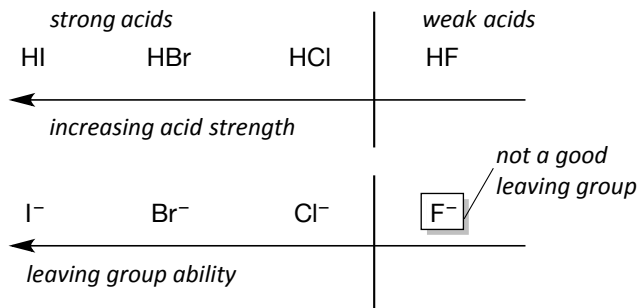
- 1) utility → alkyl halide → alcohol, ethers, thiols
- 2) reagents → weak, non-basic nucleophile
- 3) conditions → protic solvents
- 4) mechanism → cationic, stepwise
- 5) stereochemistry → loss of configuration
- 6) regiochemistry → possibility of carbocation rearrangement

Since the geometry of the carbocation is planar, attack by the nucleophile could occur from either side, producing two products.

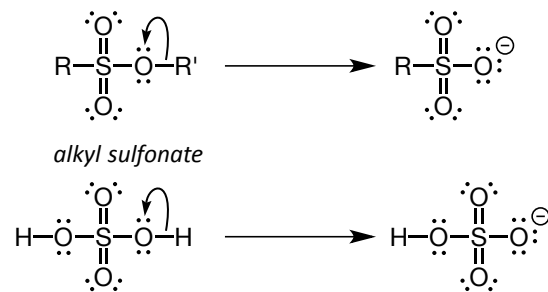
In this case, if both products form in equal proportion, a racemic mixture will result. However, after dissociation, ions can be trapped as an ion pair in a solvent cage. An ion pair can lead to a nucleophile preferentially attacking one side of a carbocation versus another.

Structures (remaining structures identical to lecture 20A)

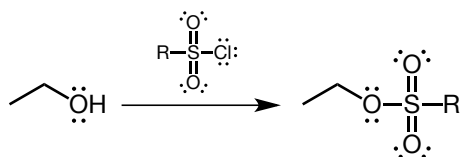
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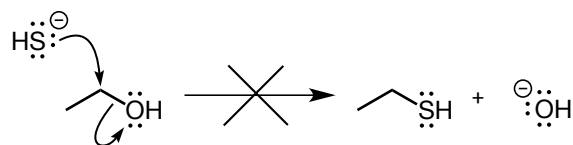
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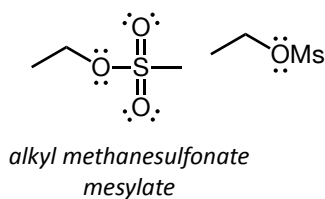
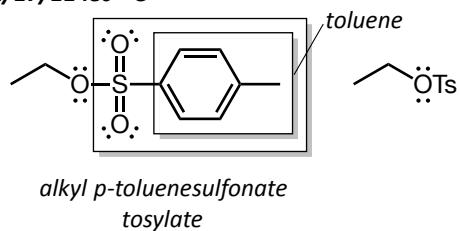
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