

## Lecture 20A • 11/16/11

### Solvents in Sn2 reactions

What is a polar aprotic solvent? Aprotic means having no easily-removable protons – it's non-acidic. It also, to some degree, is associated with this idea that whatever protons you have are unlikely to undergo hydrogen bonding. Let's discuss why aprotic solvents are the best choice of solvents for Sn2 reactions. Think about what the mechanism of an Sn2 reaction is: a nucleophile goes charging through solution, attacks the substrate, kicks off the leaving group at the same time that nucleophile comes in. That nucleophile does have to make it through the solvents, so what if you had a solvent that interacted a lot with that nucleophile. It could prevent the nucleophile from being able to attack.

For example, if you talk about order of reactivity or nucleophiles, we did discuss about polarizability versus basicity. Out of the halogens – fluorine, chlorine, bromine, iodine – which one would you say should be more reactive? Iodine, in terms of polarizability, but what does the solvent have as far as an influence on reactivity, or does it? What is the effect that solvents have? Because fluorine is basic, does it mean that's a better nucleophile or a worse nucleophile, if solvent effects weren't there? Fluorine, in an aprotic solvent, ends up being the better nucleophile, in this case because of fluorine's basicity, the fact that you do have that tightly compacted negative charge, but it has decreasing nucleophilicity for fluorine if you're in a protic solvent. It is related to fluorine and the other ions being surrounded by solvent.

Let's say we took an extreme case like water. Water can fairly easily surround the fluoride ion, because the fluoride ion is not very large in comparison. If you have a big iodine, though, then it is harder for the water molecules to be able to surround it and prevent that iodine from reacting. When you're comparing just the halogens, it does turn out that yes, polarizability does matter, but that argument usually comes up when you have two different nucleophiles that have identical structures, the only difference being whether you have something like an oxygen or a sulfur. For halogens themselves, fluorine being the tighter negative charge amongst those halogens, it's normally supposed to be the better nucleophile. But, depending on the solvent that you use, that nucleophilicity can change. What I've drawn here is what is referred to as a solvent cage, or solvation sphere. Solvation is the process of surrounding something with a solvent. A small ion like fluorine easily gets surrounded by the solvent, which prevents it from reacting with the substrate as easily. Small, compact ions like fluorine can easily be surrounded, particularly by protic solvents – things that would have these hydrogens that could have some kind of interaction with something like fluorine – which can interfere with fluorine being able to attack a substrate in an Sn2 reaction. If we list the four main hydrogens, it turns out that increasing nucleophilicity is towards fluorine – if we're not in one of these protic solvents. If we do have a protic solvent, which is going to interfere with that nucleophile's approach, then that's why we have the reverse trend, where iodine becomes more nucleophilic because it's not as trapped by the solvent.

There are two good examples of polar aprotic solvents – DMSO, which stands for dimethylsulfoxide, which looks kinda like acetone, except that it has sulfur at the junction with the oxygen instead of having a carbon; note the lone pair that is there, that is a very frequently missed part of the structure, the lone pair on sulfur. DMSO has some interesting properties that I've never tested, since DMSO does have some toxicity, but apparently, it so well absorbs into the skin, that a trick that apparently you can pull is if you get a little garlic or onion or something like that, rub it on the skin, put some DMSO on it, supposedly you can taste it, because it is pulled through your skin and ends up in your tongue. I don't know if that's just a story we heard back when we took chemistry, but it is very true that DMSO is readily absorbed through the skin, so you have to be somewhat careful for that reason when you use. Another very common polar aprotic solvent: DMF, which stands for dimethylformamide. An amide is a derivative of a carboxylic acid. A carboxylic acid is a carbonyl with an –OH hanging off of it. If you replace that –OH group with a nitrogen, that's an amide. Formamide is a one-carbon compound. That name comes from formic acid, which that name comes from formica, which is Latin for ant. The compound that's partly responsible for the sting of some ants, formic acid, which formaldehyde comes from. Formaldehyde, instead of a nitrogen being there, having a hydrogen instead. Dimethylformamide means an amide where you've put two methyl groups on the nitrogen. Technically, the name is N,N-dimethylformamide, showing that the two methyl groups are on nitrogen, instead of being on a carbon. Two very common lab solvents.

What we're going to soon start worrying about is when we write out a reaction, not a mechanism, per se, but just showing synthetically what's going on in a reaction, soon you are going to be responsible for knowing solvents. For an Sn2 reaction, a safe answer always to give right now for a solvent: DMF. Very common, very inexpensive, works well for [many] Sn2 reactions. Something like water, ethanol, other things that have protons that could undergo extensive hydrogen bonding, those would make very poor solvents. Water, alcohols; carboxylic acids would be about as bad of a thing you could use as a solvent, because remember that many nucleophiles are bases. When you're doing reactions, you've got to be careful of solvent, because if you take something that's super duper basic, what if it reacts with the solvent itself? This is the fourth of our four factors.

We had substrate – which, to summarize, for Sn2 reactions, primary substrates are better than tertiary because of what two-word property? Steric hinderance: there's less steric hinderance at a primary group than a tertiary, so primaries react. We talked about different nucleophiles.

What makes a good nucleophile for an  $S_N2$  reaction, what type of nucleophiles do we tend to have? Basic nucleophiles. They need to be good nucleophiles, meaning they need to want to attack a positive charge. Many nucleophiles are basic. What about leaving groups? What are good leaving groups? Conjugate bases of strong acids – things that wouldn't want to turn right around and react as soon as they kicked off. Now here's the fourth aspect, which is that you want to use polar aprotic solvents, which we've discussed the aprotic part of it, meaning you won't have something that will interact with the nucleophile. We'll later make a reaction coordinate diagram for why a polar solvent helps.

Let me do one more little bit of review, which is to go over the six aspects of this reaction.  $S_N2$  reactions, in general, are used to convert mostly alkyl halides to some other group, usually an alcohol or an ether. We already talked about the types of nucleophiles, those are the reagents that we've used. The conditions would be to use a polar aprotic solvent. This reaction occurs with inversion of configuration, and it is regiospecific, because the attack only occurs where the leaving group is.

Why are those solvents good? They're polar, so having a sulfur-oxygen bond or that carbonyl, those are relatively polar bonds, compared to something that's just a plain hydrocarbon. None of the hydrogens on there are acidic, and none of the hydrogens are likely to undergo hydrogen bonding because we only have methyl groups on that first solvent, carbon-hydrogen bond not very polarized, then that other one, we have methyl groups on the nitrogen, those aren't acidic almost at all.... We talked about the hybridization effect on acidity, that a hydrogen on an alkane is less acidic than a hydrogen on an alkene is less acidic than a hydrogen on an alkyne. If you wanted to think of that carbon-oxygen bond being like a carbon-carbon double bond, you would still say that hydrogen there is not really acidic at all; that's why they both make good solvent. It doesn't make them basic; in fact, formamide won't be basic because that lone pair is involved too much in conjugation with the carbonyl. DMSO is not really basic. Lack of acidity does not mean basicity; it just means the hydrogen doesn't want to come off. Just because a hydrogen doesn't want to come off doesn't mean that the compound wants to pull another hydrogen towards it.

Can the nucleophile be the substrate itself? Yes; let me show you something like that. If you used sodium hydride, NaH, hydride tends not to be very nucleophilic, but it is very basic. What could happen is an  $H^-$  could pull a proton off of a molecule like this, an alcohol. If it did that, though, that will generate what is known as an alkoxide – negative-charged ion that can be produced from an alcohol. That alkoxide could then swing around and attack and kick off the bromine that's one position over from it. It ends up forming a molecule called an epoxide. That is an intramolecular  $S_N2$ . It is a trick often used to create epoxides.

Let's get to  $S_N1$  reactions. Let's do a mechanism for the  $S_N1$  reaction. I showed you one particular leaving group that I'm quite fond of. Besides halogens, besides bromine, chlorine, and iodine – let's remind ourselves, why is fluorine a poor leaving group? Because it's the conjugate base of a weak acid. Fluoride's basic, which is why it's a good nucleophile. Saying it's a good nucleophile does not automatically mean it's a bad leaving group; don't confuse that. But fluoride is a poor leaving group because it wants to just hold on to that carbon that it's bound to. What's some other non-halogen leaving group that I discussed? Sulfonates. Let me give you specific examples of these sulfonates. This could be the substrate for an  $S_N2$  reaction as well, depending on what R is. This is an alkyl para-toluenesulfonate. Para-toluene – toluene is benzene with a methyl group on it. You can identify the toluene portion of it, but it's got a substituent on it as well; this much is toluene. Having an S with three oxygens on it, that turns it into a sulfonate functional group. This thing comes off super easily; this is often a better leaving group than even the halogens are. Why? Because once it comes off, you make an ion that's got all kinds of resonance in it. That's partly why sulfuric acid itself is so acidic. Realize that if I substitute the toluene with an  $-OH$  group, then this is sulfuric acid that we would have. Sulfuric acid, incredibly strong acid. Sulfonates or sulfate either one, ions that therefore are not at all basic and perfectly comfortable being ions in solution. That makes it an excellent leaving group. Instead of going around saying p-toluene sulfonate, though, there's the short name for it: tosylate. There's its close cousin, methanesulfonate; this is an alkyl methanesulfonate. [comment on form of nomenclature] If it dissociated, it would also make something pretty stable – again, similar reasons, all kind of resonance. [review of effects on acidity] If what you produce – like this – end up having a lot of resonance, it makes it easier to make. That's also part of the reason that this ion comes off so easily, you can just make a resonance argument. Resonance won't occur – not productive resonance – until the dissociation happens. The short name for this, mesylate.

Just to show you why this is such an important group: you can react an alcohol with a molecule whose short name is tosyl chloride. Without getting into the mechanism, just pretend that chlorine's a leaving group and that an alcohol, for this molecule, ends up being nucleophilic enough that it can displace the chlorine. Sulfur here, you can imagine, is super, super, super, super duper delta positive, because it's got two oxygens and a chlorine all hooked up to it, so it makes it really attractive for the alcohol to attack, even if the alcohol's not negatively charged. The end result of these two compounds reacting is a tosylate. Let me show you now this abbreviation:  $-OTs$ . The Ts stands for the rest of this portion of the structure. There are actually several groups – dozens of them – that organic chemists get tired of writing down all the time, so they abbreviate. Notice that it doesn't include that last oxygen that's connecting over. Ts can be used as a legitimate abbreviation for the rest of that – just like ethanol, Et; methanol, Me; propanol, Pr; butanol, Bu. Notice that in the same way I did with the tosylate, these abbreviations don't include that oxygen itself. By extension, then, I could use Et to mean ethyl anywhere; I could use Me to mean methyl anywhere.

I want to show you an  $S_N1$  reaction that did not involve three steps. When I showed you the mechanism earlier, we had an alcohol as our nucleophile. But alcohols, when they make new bonds, start off positively charged, so there's this last step of deprotonation that happens when you have an alcohol. Not always true in an  $S_N1$  reaction, and if I'm trying to make sure you know what an  $S_N1$  reaction is, that's why I want to show you an example that does not involve an alcohol. So let's say I have mesylate, and I react it with something like sodium iodide. You might say iodide: isn't that negatively charged? Yes it is, but it's not basic. All of the other nucleophiles that we're going to see for  $S_N1$  reactions are actually going to be poor nucleophiles; there's a reason for that. What can occur here is that, since we have a tertiary position, this can go ahead and form a carbocation. Why? Because you get more extensive hyperconjugation in this carbocation than you ever could with a primary or a secondary. We're going to have the opposite substrate effect that we have here for the  $S_N2$  reaction. You form that carbocation; if there is iodide floating around in solution, it could now come in to attack. You might ask: doesn't that mean that the reaction can go backwards? Could  $I^-$  then pop back off? Yes, but sulfonates are not good nucleophiles, so this reaction is likely to go in the forward direction.

Now I can write a reaction coordinate diagram from this. Overall, let's say that the reaction is exothermic. There's going to be an intermediate, though that's higher in energy than either the reactant or the product, because you're making a carbocation, you're breaking a bond. That first step, in fact, is the more difficult step of the reaction, so it's going to have the larger activation barrier; then, a smaller activation barrier to continue on to the product. Let's try to draw a transition state structure for the two transition states in this reaction. You've already seen the mechanism up above. Normally, in writing a mechanism, you don't worry about the structure of the transition state. We're just worrying about it in this case so we can get into discussing certain aspects of the reaction. Transition state one, what would it look like? Energetically, it's closer to the intermediate, which is the carbocation. It's going to look kinda like the carbocation, except that we'll have still part of the bond to the original leaving group. Ms is the same as mesyl, which is where mesylate comes from. That's transition state one; what would transition state two look like? It would look mostly like the carbocation, cause the transition state is closer in energy to the carbocation. In this case, it doesn't really give us that much information. The  $S_N2$  case, the transition state structure could be part of our way of rationalizing why inversion of configuration occurs for  $S_N2$ ; for  $S_N1$  we have a completely different stereochemical result.

To try to put some structure to this discussion, let's review the six aspects of this  $S_N1$  reaction. What is its utility? Same as  $S_N2$ : to convert an alkyl halide to one of a number of functional groups, the most common ones of which will be alcohols and ethers. What are the reagents? Normally, we use weak, non-basic nucleophiles. [ $S_N1$  versus  $S_N2$ ] You eventually need to be able to recognize that, ooh, that reagent, that's hydroxide, that's basic, that's a strong nucleophile, that's going to make  $S_N2$  happen [with secondary substrates], or, ooh, water, not a base, not a great nucleophile, not powerful enough to push a leaving group off, so it has to wait for a carbocation to form. That's actually why you need non-basic, weak nucleophiles for an  $S_N1$  reaction, because if you have a really reactive reagent, it won't wait for a carbocation; it'll try to do some other reaction. It's only if the reagent itself is not reactive that it can wait around for the carbocation to form. Once it forms, ooh, there's that positive charge it would want to chase, and then reaction begins. We need weak, non-basic nucleophile, so that the carbocation has a chance to form. What about the conditions? The conditions have to do with the solvent. Usually, we use protic solvents. In fact, the solvent is usually the nucleophile. What about the mechanism? We've got that right above. What about stereochemistry? To summarize, you have loss of configuration. What about regiochemistry? Technically, if we have a carbocation intermediate, we have hydride shifts that are possible. Hydride shifts and methyl shifts are kinda the same effect. Better way of general in saying it: carbocation rearrangement.

Let's look at the stereochemistry question. If I had some tertiary center that was chiral, if I allowed the leaving group to leave, make the carbocation that is  $sp^2$ -hybridized and planar. Since the geometry of the carbocation – the important intermediate – is planar, attack of the nucleophile can occur from either side, producing two products. To continue that example, if I had a tertiary alkyl halide, and I reacted it with a nucleophile like ethanol – a weak nucleophile, not negatively charged; still has a lone pair on the oxygen, still has an oxygen that's delta negative. It may not be negatively charged, but it is delta negative, so it will react. If I don't include the mechanism, if I just show the products, here are the two products that will result. If we form the products in 50/50 mixture, what is that called? Racemic. This reaction will not always make a racemic mixture. If both products form in equal proportions, the mixture will be optically inactive, because it is racemic. But it won't always happen, that it'll be 50/50. Even in a case like this where there's not much around the carbocation to influence the reaction. Why don't [racemic] mixtures always form? It's back to the solvent, the effect of the solvent. Imagine this: carbocation forms, the ion comes off, but what if the solvent surround that pair of ions, keeps the ions somewhat associated with each other. In other words, the bond breaks, but the ion doesn't just go off into solution, it kinda hovers there right there with the molecule – that's called an ion pair. They're ions, but they're paired up at the same time, so they're not bonded, but they're not separate either. If you have an ion that's floating above the reaction site, the carbocation, then that ion itself can block incoming molecules, making attack from the other side slightly more likely. Since it is dissociated, it's not that the ion is permanently there blocking the approach; the ion can move over and the molecule can come in to attack. So, you'll get two products, but you won't get 50/50; maybe you'll get 60/40 or something like that, so it could be skewed a little bit. You still produce two products, but you don't end up with a racemic mixture. If both products form in equal proportion, the mixture will be optically inactive, which is because it's racemic, however, after dissociation, ions can sometimes form ion pairs in solution. When this occurs, one side of the carbocation in this reaction would be somewhat blocked.

Imagine this: we have a plane; let's say we have our molecule to be attacked in it. Here's a p orbital, and here is the ion floating around above it. This attack is slightly more likely from below. Bromine's only going to dissociate to one side; that means the other side is more open. When this occurs – this meaning that the ion pair forms, one side of the carbocation would be somewhat blocked, which would result in a mixture with two products, but not in exactly equal proportion.

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#### Polar aprotic solvents for $S_N2$

Aprotic – having no “easily” removable protons (non-acidic) → those hydrogens that are present are unlikely to undergo hydrogen bonding

solvent cage – solvation sphere – small, compact ions like fluorine can easily be surrounded by protic solvents, which can interfere with fluorine being able to attack a substrate in an  $S_N2$  rxn.

poor solvents for  $S_N2$ : water, alcohols, carboxylic acids

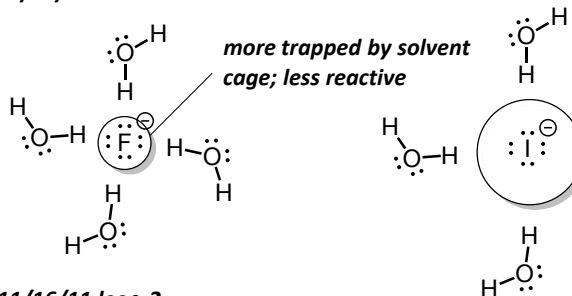
- 1) utility → alkyl halide → alcohol, ether
- 2) reagents → weak, non-basic nucleophile
- 3) conditions → protic solvents
- 4) mechanism
- 5) stereochemistry → loss of configuration
- 6) regiochemistry → carbocation rearrangement

Since the geometry of the carbocation (the important intermediate) is planar, attack of the nucleophile can occur from either side, producing two products.

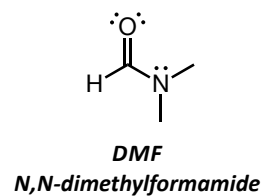
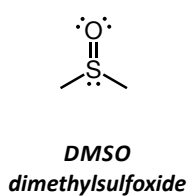
If both products form in equal proportions, the mixture will be optically inactive (racemic). However, after dissociation, ions can sometimes form ion pairs in sol'n. When this occurs, one side of the carbocation would be somewhat blocked, which would result in a mixture with two products, but not in exactly equal proportion.

Structures

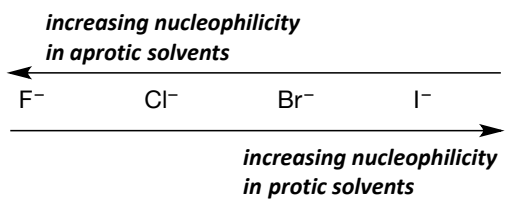
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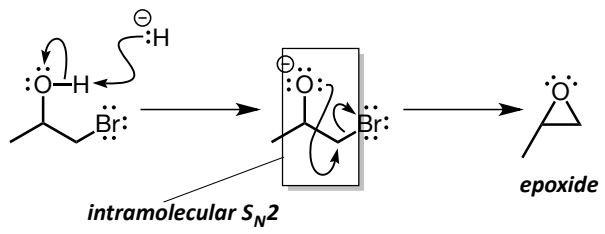
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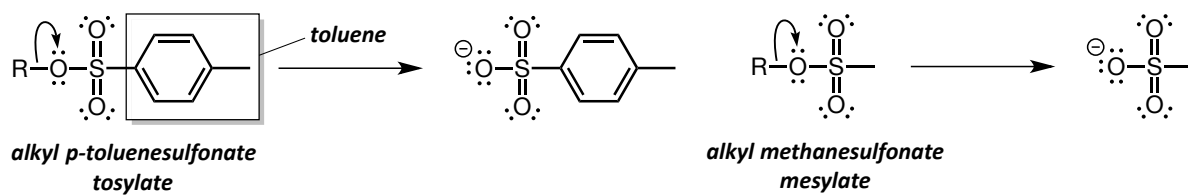
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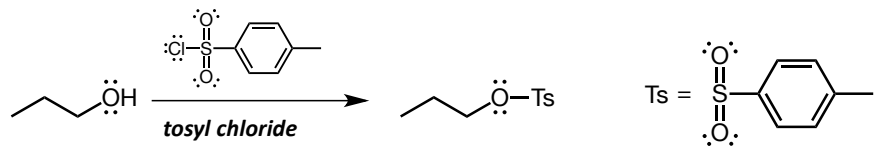
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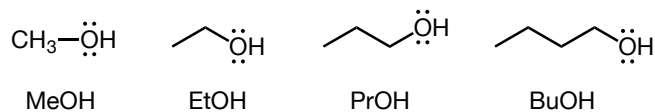
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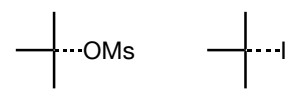
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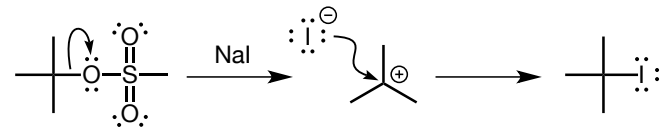
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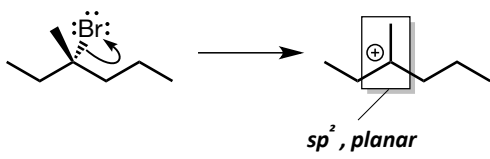
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