

## Lecture 21A • 11/18/11

[quiz review][factors affecting acidity – hybridization; inductive effect; resonance][Sn2 and Sn1]

We saw an example mechanism for an Sn1 reaction. We need to know the utility is to make alcohols and ethers, just like the Sn2 reaction. Why do we need the Sn1 and Sn2 reactions if they have the same synthetic utility? That's because primary substrates can't do Sn1 and tertiary substrates can't do Sn2, so both happen because of the types of structures involved. What are the reagents used? Reagents need to be weaker nucleophiles that allow the carbocation time to form. Solvents, it's going to be polar protic solvents that are best for Sn1. Mechanism, you saw. We talked about stereochemistry, the fact that, in principle, you should get racemic product mixtures, if you start with only one stereocenter and you do an Sn1 reaction. We did also talk about the formation of these ion pairs; that ion pair could make one side of what should be just a plain planar intermediate, one side more favorable to be attacked than the other. The one thing that we didn't see a good example of is what happens in regiochemistry - rearrangements are possible because Sn1 reactions are cationic reaction [so] you're gonna get carbocation rearrangements. That falls under regiochemistry.

Imagine that we have this: a secondary alkyl halide, where that secondary position is next to a tertiary position. Let's say that you were trying to do an Sn1 reaction, the first step of which would be for that halogen to dissociate. If it were to do so, you'd end up forming a secondary carbocation, which isn't as good as a tertiary. But, it is possible for that hydrogen to move over to form a tertiary carbocation. Once it's formed, now we could have the attack of a nucleophile – a simple nucleophile which I've used often, water. In this specific example, since there's two methyl groups attached to the carbocation position, we're not going to make a stereocenter, so in terms of stereochemistry, we're only going to form one unique product in this case. There is this last deprotonation step that occurs; we end up with an alcohol. Point being, we end up with a tertiary alcohol, even though we started out with a secondary substrate; that's because of this hydride shift.

We covered the six aspects of the reaction. [flashcards] Let's switch now to talking about the four factors that could affect the reaction: substrate, nucleophile, leaving group, and solvent. As far as substrate, we had already talk about how tertiary substrates are much more reactive than secondary than primary, which are really about the same as methyl for Sn1 reactions. For rough numbers, we had a relative rate of 1 for primary, something like 10 or 12 for a secondary, and something like a million in terms of relative rate for tertiary. That's how much more favorable hyperconjugation makes the formation of a tertiary carbocation versus the primary or secondary. In the order that I've written these substrates, it would be this direction that we have reactivity in Sn1 reactions. Tertiary substrates are far more reactive in Sn1 reactions than others since tertiary carbocations are far more stabilized by hyperconjugation. We have talked about an example where a primary carbocation can form if it's got something next to it that helps stabilize that – what I'm specifically referring to is the benzyl case. I could take something like benzyl bromide [and I'm] going to be able to get dissociation, because even though it's a primary, it's not dependent on hyperconjugation for its stability; it's going to be plain old conjugation that occurs. Even though this is a primary carbocation, it forms easily, due to conjugation with the neighboring benzene ring.

After it forms, we could have attack from a nucleophile; just for fun, let's have a nitrogen-based nucleophile, which should be a better one than oxygen since this compound ends up being basic compared to one with oxygen, which should correlate to a bit more nucleophilicity. Much like if I had an oxygen-based nucleophile, because this started out neutral, once it does attack, it's going to initially be positively charged; we'll have a deprotonation event, and we end up with our product. For reasons similar to this, if we had an allyl substrate – this is allyl bromide; crotyl is a special name that's allyl that's got [a methyl group on it]. But as far as the position away from the double bond, that's what allyl means. Any general structure that has this feature in it will also undergo Sn1 reactions, because forming an allyl carbocation is similar favorable. I'll go back to water being the example nucleophile; after deprotonation, we end up with an alcohol. Allyl substrates are also reactive due to conjugation.

Allyls might be reactive, but vinyl halides. Vinyl means the double bond position itself; if you put something on the double bond, that is called the vinyl. You might have heard of PVC, polyvinyl chloride, vinyl chloride itself would be this molecule where X is chlorine. Vinyl means attached to the double bond. It turns out a molecule like vinyl chloride will not undergo an Sn1 reaction. There's two reasons why this is true: one is an argument about bond strength. Think about this: hybridization. If you have an orbital like an sp orbital that's made up of more of an s orbital, if you put electrons in that orbital they'd be held more closely to the nucleus. When we discussed it, we were talking about free electrons, a lone pair. But the same kind of logic could be used to talk about what kind of bond you have in a sigma bond, what strength you might have when that orbital gets connected to something else. It turns out that a hydrogen connects to an alkyne – a hydrogen overlapping with an sp orbital – that's a stronger bond than sp2, than sp3, because electrons get held more closely to carbon. Let's turn that whole story backwards, because what we're talking about is the formation of a carbocation, so we're not putting electrons in; we're exposing the nucleus. Because, in an sp orbital, the electrons would effectively end up closer to the nucleus – that's why they're lower in energy, that's why it's easier for it to handle a negative charge – that means that if you didn't have the electrons, the positive charge is more exposed, less stabilized you could say. For an sp orbital, a positive charge is a worse thing than for an sp2 than for an sp3. We've taken an sp2-hybridized system and tried to make an sp carbocation.

This sp-hybridized orbital is just not favorable enough to bear that positive charge, compared to other systems we've seen so far where you have an sp<sup>2</sup> orbital. So, vinyl carbocations do not form because the positive charge cannot be as well tolerated by orbitals that have more s character. Sp orbitals are better in tolerating negative charge. Wherever something is better with being negative, for the same reasons, that almost always means it's worse at being positive; if something's really good at being positive, then for the same reason it's not good at being negative. Sp hybrids better tolerate negative charges but poorly tolerate positive charges.

It turns out, in S<sub>N</sub>2 reactions, vinyl substrates also aren't reactive. We talked about how a nucleophile would not be able to pass through the ring of benzene. That's true in general for other compounds with double bonds, because effectively what ends up happening is the electron cloud from the pi bond itself, because it's not sitting there right between the atoms, it's actually above and below the atoms, that pi bond ends up repelling the nucleophile, preventing it from reacting. Vinyl substrates do not undergo S<sub>N</sub>2 reactions because the electrons in the pi bond repel the nucleophile.

Let's move on to the other factors. Next one is nucleophile. What makes a good nucleophile is really independent of what kind of reaction's going on. Good nucleophiles, in a sense, for S<sub>N</sub>2 reactions are the same as for S<sub>N</sub>1 reactions – the problem is, we don't want a good nucleophile for an S<sub>N</sub>1 reaction. Why? Particularly if it's a basic nucleophile, it just wouldn't wait around for the carbocation to form. In fact, one of the major side reactions you're going to get is elimination, formation of an alkene. If you had a strong nucleophile, particularly one that's basic, it's just not going to let the S<sub>N</sub>1 reaction happen. For S<sub>N</sub>1 reactions, in terms of nucleophile, poor nucleophiles – particularly non-basic nucleophiles – are preferred, since S<sub>N</sub>1 reactions depend on the carbocation having time to form.

Third factor, leaving groups. Here, exactly the same thing that makes leaving groups good for S<sub>N</sub>2 is the same for S<sub>N</sub>1; in fact, it's even more important for S<sub>N</sub>1, you could say, because S<sub>N</sub>1's a unimolecular reaction – it only depends on the substrate, which means if you have one [leaving group] versus another, that in itself is what's going to affect reaction rate. It doesn't matter what kind of nucleophile that you have, because it's not in the rate law. Leaving group, being part of that substrate, really affects the rate of an S<sub>N</sub>1 reaction. Good leaving groups are conjugate bases of strong acids.

The last thing that we need to talk about is solvent, which is a fairly easy one for an S<sub>N</sub>1 reaction. For S<sub>N</sub>1 reactions, polar protic solvents are normally used; in fact, the nucleophile is often the solvent itself. Why are polar, protic solvents used for S<sub>N</sub>1 reactions? Cause you have to make a carbocation; if you've got something that's protic, that means you've got something that could do hydrogen bonding, which means you've got an atom on there that's got a delta negative on it. It would be able to help stabilize a positive charge as it forms. Why is the solvent often the nucleophile? Why can't you make the solvent the nucleophile in an S<sub>N</sub>2 reaction? Seems like in both cases, if you flood a reaction with reagents, you're going to force it towards products. In S<sub>N</sub>2 reactions, nucleophiles are usually ionic, which means they're gonna usually be solids; for S<sub>N</sub>1 reactions, you have things like water or ethanol, things that would be liquids because they're not ionic; it becomes easy to make them both the nucleophile and the solvent for an S<sub>N</sub>1 reaction.

Let's move finally into eliminations. Let's say that we had the case of a tertiary substrate that we did try to throw a basic nucleophile at, like hydroxide. You might think: ok, hydroxide's a good nucleophile, it would be able to really attack a carbocation if it formed. But hydroxide, besides being nucleophilic, it's also basic – basic meaning it's really able to pull a proton off of something. Let's think of it this way: in this substrate, we already have a delta positive center where than bromine is. That delta positive center's going to have a little bit of a tug on the carbons that are attached to it, which in turn means the hydrogens that are attached to those carbons, they're going to feel a little bit of tug from that delta positive carbon. What if a hydrogen came along and just sorta helped things along, pulled the hydrogen off so that the bond that was there ends up sliding over and attacking the leaving group, kicking it off. That's an elimination reaction.

We have two different neighbors, so I'm going to show you two different possibilities; they'll both be the same mechanism, though. One possibility is hydrogen is attacked by hydroxide; that bond is going to break, and the lone pair that would be left could fall right next door and attack a bromine and kick it off. If that were to occur, we would make this product. Another possibility is maybe one of the hydrogens from one of the methyl groups could get pulled off instead – it reacts, the pair ends up falling into the leaving group; same last part of that step, then, the leaving group comes off, and we've again formed an alkene. The hydrogen does have to be on a carbon right next door in order for this reaction to be able to occur. We'll see a transition state in a moment that explains why the reaction can only happen in these two cases. The lone pair can't hop over a molecule and make a bond that far away; it's just not possible.

One of these alkenes ends up being more thermodynamically favorable than the other one. It turns out to be the one that has more substituents on the alkene itself; in this reaction, this will therefore be the major product. This is E2. More of this product forms because it is thermodynamically more favorable. Why? The quickie answer is to say hyperconjugation. Think of it this way: hyperconjugation helped stabilize radicals, stabilize carbocations, stabilize things that have p orbitals in them. A double bond we model by saying that's two p orbitals that are stuck together. If, on the double bond, all you had was hydrogens around it, those hydrogens can't overlap with the p orbitals because they're at 90° angles.

But put a methyl group on it, now you have carbon-hydrogen bonds that, as they rotate around, they'll line up with the p orbitals, and so then you'll have hyperconjugation possible. The more substituents you put on an alkene, the more conjugation, the more stable that alkene ends up becoming. Let me define this as an E2 reaction, which means bimolecular elimination. Why is it called E2, bimolecular? Because no matter which one of these two outcomes I think is more likely, both of them involve two molecules at the same time: the incoming nucleophile and the substrate that's getting attacked. Since there's only one reaction step, both of these molecules are involved in that one rate-limiting step. Similar reasons as why Sn2 is called Sn2, because there are two molecules in the rate law. This is also a concerted reaction because everything happens all at once.

I want to say something about this pattern of elimination. There's something known as Zaitsev's rule, which is: in eliminations, the more heavily substituted alkene is normally formed in greater proportion. There's a fairly straightforward, hand-waving argument for this. The more stable the product that you make, the more downhill in energy it is, then, generally, that would correspond to something that has a lower activation barrier, kinda like what we saw with the free-radical halogenation. The more stable product – kinda like the more stable radical we made in that case – the one that's more likely to occur. Zaitsev's rule doesn't away apply. Let me draw up this reaction coordinate diagram to get you thinking about something. Let's say you have a reaction where you have one set of reagents that could form two different products, just like in this case. Let's say those two different products are fairly different in energy from each other. To continue this example, what if, in order to get to the more favorable product, the thermodynamically more stable product, it actually had a tougher activation barrier; we had a curve that look like this. Versus making the less-stable product, but maybe it has a pathway that has a lower activation barrier. At high temperatures, or, particularly, if the reaction's reversible, eventually thermodynamics does win out. But let's say that we're at low temperature. There's not a lot of energy around. If you're faced with two possible reaction pathways, and not a lot of energy to do them, wouldn't it make sense that the lower barrier should be the reaction occurs more quickly, because lower activation energy means it's a faster rate of reaction.

What if you had exactly this situation, then; might be able to form a most stable product, but it's harder to do, so at low temperature, maybe the less stable product would be the one that's favored. This is something known as kinetic versus thermodynamic control. It comes up exactly in this case: if I take the same alkyl halide and I use a really hindered nucleophile – up to this point, we've been focusing on whether the substrate was hindered or not; now I'm focusing in on the nucleophile being hindered. This is known as the t-butoxide ion; we haven't named alkoxides yet. An alkoxide, that's short for an alkane oxide, taking an R group and sticking it onto an oxygen. Same way that name's produced, we could say methoxide, ethoxide, propoxide, butoxide, for one, two, three, and four carbons. This was a t-butyl group, so that's why it's called t-butoxide. But that ion has got so much steric hinderance around it that when it tries to go out and attack something else, it realizes it has steric issues as well. If it's going to be thrown at this particular alkene, it could try to go after the hydrogens on the secondary position, but those hydrogens are also more sterically hidden, versus the primary hydrogens. Maybe attack at the secondary position would make the more favorable product, but in terms of kinetics, it's instead going to attack the more open, the more accessible primary position, even though that's going to make the less-favorable product. This would be called the anti-Zaitsev product. Zaitsev rule says more substituted alkenes will form, but this is a way that you can force the opposite to occur. If a nucleophile is very sterically hindered, it can cause the formation of a less stable alkene, due to kinetic effects. That's because more hindered nucleophiles make it more difficult to remove more hindered hydrogens.

Let's tackle the six aspects of the reaction. This is for the E2 reaction specifically; there's also an E1 reaction. Once we've learned all of these reactions, the natural question is: when is E2 going to happen, versus E1, versus Sn2, versus Sn1. We have the synthetic utility, which is very clear in this case: it is to convert alkyl halides or other similar substrates like sulfonates into specifically alkenes. What are the reagents used? Strong and, more importantly, basic nucleophiles; you want something to be able to pull that hydrogen off. What are the reaction conditions used? In terms of solvents, it's still going to be polar aprotic solvents that work best; we don't want something interfering with the nucleophile or the base trying to attack that hydrogen, so we don't want something that has hydrogens that might appear tasty to that nucleophile.

Stereochemistry – there are a couple of stereochemical effects in this reaction. Let me construct a diagram here of some random tertiary substrate, so I've got two R groups attached to the same position as the leaving group; let's say the two R groups are alkyl groups. Maybe they have hydrogens, maybe they don't; only the hydrogen I've got written in I'm going to allow to react. To review the mechanism for E2, what we'll see is the hydrogen gets removed. That lone pair will swing around and push off a bromide. What would the transition state look like? The halogen's leaving so we'd write that with a dotted bond. We still have the R groups that aren't going anywhere. There is the alkene that is starting to form. Then, there's the hydrogen that's starting to be removed. Let's draw a very small partial SMOG for exactly this situation; let's just look at the hydrogen-carbon bond and the halogen-carbon bond. To begin with, they were both sp<sup>3</sup>-hybridized. Hybrid orbitals actually have a node through them that I'm going to write in. Why? Because, what effectively is happening as this alkene is forming is these sp<sup>3</sup> hybrids are going to start overlapping and start turning into a pi bond; they're going to turn into p orbitals, which means this is only really favorable if the orbitals are like this, where they're, in some senses, parallel. Technically, they're antiparallel to each other, because they're pointed in opposite directions, but still, they're able to overlap because they're eclipsed, to use that word. If you have the orbitals at an angle to each other, the overlap would not be anywhere near as great. That would mean there would be no reason for that hydrogen to come off, cause the pair of electrons that was there would not be able to overlap well with the leaving group next door. Instead of antiparallel, the term here is antiperiplanar.

Syn versus anti, those are short for synperiplanar and antiperiplanar. What's this periplanar mean? That they're not pointed opposite each other, they're opposite from each other one position over. Antiperiplanar is the full name for the relationship between two groups separated that are opposite from each other.

Could synperiplanar elimination occur? Yes, because in synperiplanar orientation, they'd still at least be overlapped with each other. Here's what it would look like. Here's the setup. Imagine that in the transition state, we look at the orbitals at the carbon-hydrogen and carbon-bromine bonds. We would again have appropriate overlap that could occur. This is synperiplanar. Eliminations, in general, can only occur if the hydrogen removed is synperiplanar or antiperiplanar to the leaving group.

Why does this matter? Here's a specific case. Notice in this molecule, elimination really would only be possible one direction, because to the left of the leaving group, I've got two methyl groups, which means there's no hydrogen there; no hydrogen, can't do elimination. There is a hydrogen to the other side of it, though, but will elimination occur? Will be able to get into the right configuration? Let's try drawing a chair structure for this. How are we going to make a chair structure out of this? Let me put the methyl groups in this back corner; that's going to make the bromine be equatorial, the hydrogen that's implicit there axial; that's going to make the methyl group next door axial, and the hydrogen equatorial. Are those either syn- or antiperiplanar at the moment. Neither. If we were to make a [Newmann projection] visualizing along this axis, we would say that they're gauche to each other, 60° angle, not 0° or 180°. But, what if we ring flipped? Let's write the ring-flipped structure. [caution about writing chair structures correctly]. Notice that the hydrogen and bromine are now antiperiplanar to each other. What about this case then? What if we just flipped the position of bromine? Would an E2 reaction occur for that molecule? Why does the hydrogen have to be adjacent? Because you have to have that orbital overlap. If you don't have that orbital overlap, you can't have elimination. Something that's that far down the molecule, it's just not possible.

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## 6) Regiochemistry

1) substrate – 3° substrates are far more reactive in Sn1 rxn since 3° carbocations are far more stabilized by hyperconjugation.

Even though this is a 1° carbocation, it forms easily due to conjugation with the neighboring benzene ring.

Ally substrates are also reactive due to conjugation. vinyl → attached to the double bond

Vinyl substrates do not undergo Sn1 rxns since vinyl carbocations are unfavorable due to increased s-character of the orbital (sp hybrids better tolerate – charges but poorly tolerate + charges).

Vinyl substrates do not undergo Sn2 rxw because the electrons in the pi bond repel the nucleophile.

2) nucleophile – For Sn1 rxn, poor nucleophiles – particularly non-basic ones – are preferred, since Sn1 rxns depend on the carbocation having time to form

3) leaving groups – Good leaving groups are conjugate bases of strong acids.

4) solvent – For Sn1 rxns, polar protic solvents are normally used; the nucleophile is often the solvent itself.

Eliminations – E2 – bimolecular elimination

Zaitsev's rule – In eliminations, the more heavily substituted alkene will normally be formed in greater proportion.\*

If a nucleophile is very sterically hindered, it can cause the formation of a less stable alkene due to kinetic effects (more hindered nucleophiles make it more difficult to remove more hindered hydrogens).

E2

1) utility → alkyl halides → alkenes

2) reagents → strong, basic nucleophiles

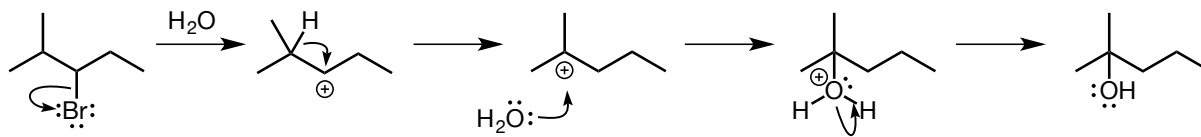
3) conditions → polar aprotic solvents

5) stereochemistry

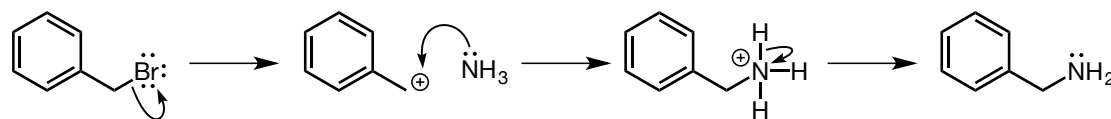
Eliminations can only occur if the hydrogen removed is synperiplanar or antiperiplanar to the leaving group.

Structures

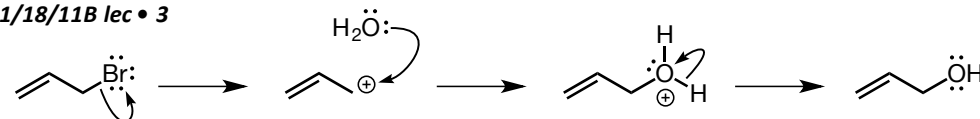
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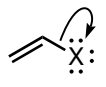
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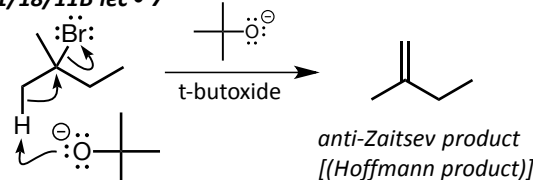
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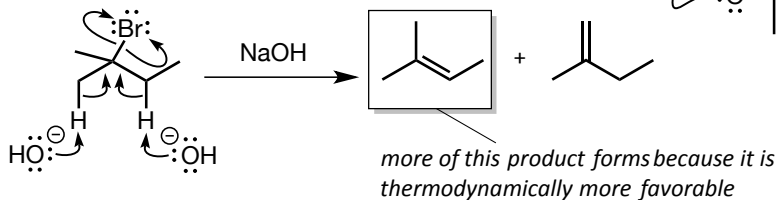
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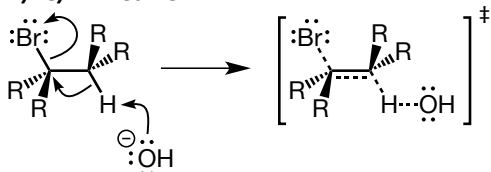
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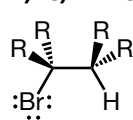
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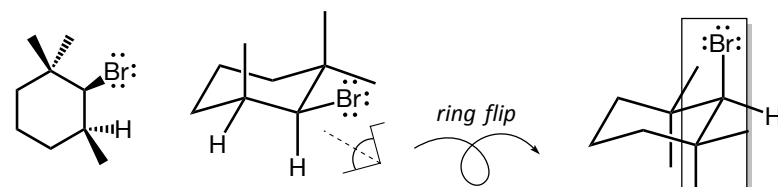
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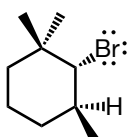
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will E2 occur?

antiperiplanar