

Lecture 21B • 11/18/11

For S_N2 reactions, because you generally have something that's basic, that's ionic; there are ionic solvents, but they're kind of a rarity. We have something like sodium ethoxide – take ethanol, pull the hydrogen off, put an ion onto it, it's going to be a solid. Most of those compounds can't be used as solvents.

The six [aspects of the reaction are:] the utility, that is make, generally, alcohols, ethers, or thiols. Reagents, they are weak nucleophiles, because if we have strong ones, they're going to cause S_N2 to happen instead. Solvents, we're going to want protic polar solvents for this reaction. We saw the mechanism; we were working on stereochemistry.

As a reminder, the S_N1 reaction, the main intermediate there is the formation of a carbocation; that carbocation is going to be planar. But, it is possible for the ions, after they form, after that leaving group leaves, for them to remain somewhat associated with each other, which can cause one side or the other to be preferentially attacked. You have the potential to form racemic mixtures, but sometimes you'll form mixtures that do have two products, but maybe you won't have a 50/50 distribution. One thing we didn't see an example of is regiochemistry, that last [aspect of the reaction].

Here's an example: a secondary alkyl halide that reacts in an S_N1 reaction – but a secondary alkyl halide that has what could be a tertiary center right next door. The first step of this reaction would be like any other S_N1 reaction, where the leaving group leaves. But, it is possible that the hydride can shift over one position, which would end up making the carbocation on the tertiary position instead. At this point, the carbocation could be attacked. In this particular example, we wouldn't make a stereocenter, so I only need to draw one product. After losing an extra proton, I end up with an alcohol. This will be the major product of the reaction, which is an example of the fact that because S_N1 reactions are a cationic type of mechanism, you're going to have rearrangement possible.

Now let's tackle those four factors that affect the reaction. Substrate – if you look at the relative reactivity of a primary versus secondary versus tertiary alkyl halide in an S_N1 -style reactions, it's something like 1 to 10 to 1000000 in terms of rates. Tertiary carbocations are just that much more favorable to form. It is because of hyperconjugation that that tertiary carbocation is more favorable. Tertiary – much, much greater in reactivity than secondary, greater than primary, which is about the same a methyl in terms of rate. Tertiary substrates are far more reactive in S_N1 reactions, since tertiary carbocations are far more stabilized by hyperconjugation. The benzyl carbocation – having this conjugation next door can make a carbocation form, even if it's on a primary position. You can get an S_N1 -style reaction on benzyl bromide itself. The key, tough point in this reaction – formation of the carbocation – is ok in this case because you've got conjugation with the benzene ring. You can have something else come and attack it, like ammonia (we haven't seen that as an example of nucleophile yet). It's a bit stronger nucleophile than water because ammonia is somewhat basic, so it's neutral so it's not as good as something like hydroxide. But ammonia could substitute. Notice the way that I drew that carbocation: recognize that if you've got a line there, the end of that line counts as a carbon position as well, so once this bromine came off, I didn't leave a line there drawn to a carbocation, cause that's not the way that you draw a structure. Nitrogen comes and attacks. Much like water or an alcohol, when that nitrogen first bonds, it's going to be positively charged, so there'll be a follow-up deprotonation step. In exactly the same way that benzyl substrates are able to react in S_N1 , even though they might be primary, allyl substituents can do that as well.

But, vinyl substrates – vinyl means something that's attached to the double bond itself. If you have a vinyl halide, it turns out it is not likely to dissociate to form a carbocation. Can you think of a reasonable reason why? I had brought up this question of acidity. One of the three factors that we had reviewed was hybridization – the fact that, if you have an sp^3 -hybridized carbon, that is not as much like an s orbital as sp^2 as sp , and the more s-like that that orbital is, the lower energy of putting lone pair into it would be, cause effectively that lone pair is closer to the nucleus. What if we turned that exact same reasoning right back around the other direction. Instead of worrying about negative charge being there, what about a positive charge, the lack of electrons being there? On an sp^2 -hybridized orbital, that positive charge would mean less exposure of the nucleus because the electrons would end up in an orbital not as close to the nucleus to begin with. You'd have more exposure with an sp^3 . The more s-character than an orbital has, because it's better at accommodating a negative charge, for the same reason, it's also worse at being able to accommodate a positive charge. Along with that, there is this argument that bonds to sp^2 -hybridized centers are stronger than bonds to sp^3 -hybridized centers, for much the same reason as why a negative charge is more stable on an sp^2 ; that lone pair's effectively held closer to the nucleus. Because of hybridization, the positive charge is just not as likely to form, both because the positive charge itself is not as stabilized, and the bond to break, to make that carbocation, is a stronger bond. Vinyl substrates do not under S_N1 reactions because vinyl carbocations are not stable. Orbitals with more s-character better stabilized negative charges but are worse at stabilizing positive charges. The pi electrons end up interfering with the approach of a nucleophile. In general, for S_N2 reactions, vinyl substrates don't react for them either, because the nucleophile is repelled by the double bond itself.

What about the other three factors? There's the nucleophile itself, then there's the solvent, and leaving group. Let's tackle the nucleophile and leaving groups first. The same things that make good nucleophiles for S_N2 reactions make good nucleophile, potentially, for an S_N1 reaction.

But remember, we don't want a particularly good nucleophile for an S_N1 reaction, because a really good nucleophile would try to do S_N2 instead. For nucleophiles, what makes a good nucleophile is independent of the reaction it's in. For S_N1 reactions, you want want poorer, or particularly, non-basic nucleophiles. The reason we need poorer nucleophiles is because the reaction depends on the formation of the carbocation; if you've got something that's too reactive, doesn't wait for that carbocation formation, then you're going to get some form of side reaction, the main one of which is elimination.

In terms of leaving groups, good leaving groups for S_N1 reactions are exactly the same ones as leaving groups for S_N2 reactions. In fact, the nucleophile itself, other than worrying about whether you might get a side reaction, doesn't matter for an S_N1 reaction, because it's not in the rate law for an S_N1 reaction. The only thing that would really change the rate for S_N1 is which kind of leaving group that you use. Good leaving groups as still going to be conjugate bases of strong acids. [table] There's a set of compounds that all have negative pK_a s; those are exactly the compounds that you've seen so far in examples for good leaving groups: HI, HB, HCl, they're some of the highest pK_a s; iodi[de], bromi[de], chlori[de] are therefore good leaving groups. Sulfonates are also excellent leaving groups.

The last of the four factors – that's solvent. In S_N1 reactions, polar protic solvents are normally used, and the solvent itself is often also the nucleophile. Why was it for S_N2 that you didn't use the nucleophile? Because, most of the time, nucleophiles in S_N2 reactions are going to be solids because they're ionic. But for S_N1 reactions, because we usually don't want an ionic nucleophile, we want something that's not negatively charged, so it's not quite as hot and reactive, therefore if it's neutral you're much more likely you're going to have a liquid. Water, ethanol, some other kind of alcohol, ammonia (ammonia itself is technically a gas at room temperature, but compounds related to amines, those also make good S_N1 nucleophiles, they're also liquids, they could potentially be solvents). Why make it the solvent when possible? Think about if this was an equilibrium situation: the greater the amount of nucleophile that you have around, the more likely you're going to push the reaction to completion. The solvent is usually the nucleophile. Because it involve things like ethanol, particularly things like ethanol, alcohols, in the grand scale of things are relatively acidic, it'd be potentially reactive with hydroxide, at least, or at the very least they extensively have hydrogen bonding, so they count as protic solvents. Protic solvents normally used for S_N1 reactions.

We've covered all of the aspects of both S_N1 and S_N2 reactions. The one remaining thing to discuss is how polar solvents help S_N2 reactions.

Here's exactly the type of side reaction you have to worry about if you're using a tertiary alkyl halide: let's say that you tried to throw sodium hydroxide at this. You might be tempted to think: ok, sodium hydroxide, it is a strong nucleophile, but let's see if you could sit around long enough and let the carbocation form on this tertiary alkyl halide. But this is where basicity comes in to play. Yes, hydroxide's a pretty good nucleophile, but hydroxide's also a base – specifically meaning it would like to remove a proton from somewhere. The position where the leaving group is, that's already a little bit delta positive, which means that there's some tug that that position has on other surrounding positions near it. You could imagine that, maybe a hydrogen next door, that bond to the hydrogen might be ever so slightly polarized towards that delta positive, just because that delta positive is there. What is a hydroxide just came along and helped finish off the job; what if you had something that came along and could just pull that neighboring hydrogen off? The pair of electrons that used to be in the bond to it could then swing around and kick off that leaving group, which would leave you an alkene. This is exactly what would happen in real life. The would not be the major product of the reaction; this is just one of the possibilities. What if, instead, we have [hydroxide] pull off another neighboring hydrogen; we have another alkene that could form. Elimination is going to be what happens because the hydroxide simply won't give the carbocation time to form. This, in fact, is known as the $E2$ elimination – bimolecular elimination.

Why's it called $E2$? Notice that, regardless of which of the products we end up thinking is going to be the major one to form, both of these mechanisms involve the nucleophile and the leaving group reacting at exactly the same time. Because this is the one and only step in the reaction, that means both of these reagents are going to be present in that rate-limiting step, which means both of these show up in the rate law. Since you have two reagents, that's why it's called bimolecular. Similar reasoning for the two in this, as for the S_N2 reaction.

Let's come back to address the question of which one of these should be more likely. It turns out that the second product that I have written is the thermodynamically more favored product. The more substitution that you have on an alkene, think of it this way: you've got these p orbitals on the p bond that can undergo hyperconjugation with the groups around it. That hyperconjugation has the same kind of stabilizing effect as it would on a radical or on a carbocation. On an alkene, the more alkyl groups you have attached, the more possibility for hyperconjugation that you have. If all you had was a hydrogen attached to a double bond, that hydrogen is pointed out at 90° to where the double bond is located. Just like when we talked about methyl groups not having any hyperconjugation, the same thing would happen if you had an unsubstituted alkene. Putting more substituents on that alkene ends up stabilizing that alkene. If thermodynamics ends up being the thing that controls the products in the reaction, because that second product is lower in energy, it's going to be the one that's more likely to form. We're going to talk about some experimental evidence showing which alkene is more stable. More substituted alkenes are more thermodynamically stable. Therefore, that second product is the most likely one to form.

The proportion is not necessarily completely lopsided; it's not like you'll get 99% and 1% of the other. In fact, the proportion can be somewhat affected by which leaving group that you use. It also can be affected by the nucleophile that you use. In general, unless you use one of these nucleophiles that purposely causes another effect, it is the more substituted alkene that is going to predominate. That principle that that's going to predominate is known as Zaitsev's [elimination]. Zaitsev's rule says in eliminations, the more heavily-substituted alkene will be the most likely one to form. There is one way to force what you'd call an anti-Zaitsev elimination, reverse of the effect predicted by the Zaitsev elimination.

Imagine this situation: what if you had two products that could form. Let's imagine that one of them is way more thermodynamically stable than the other. But let's just say that, for the sake of argument, because of the way that the reaction occurs, the transition state to get to that much more stable product, what if it's a much higher transition state than the one to form the less favorable product. In other words, what if we had a reaction coordinate diagram like this: from one starting point, here are two possible products, very different than each other in energy. The scenario I'm setting up here is: let's say to get to that much more stable product, for whatever reason, there's a high activation barrier, but then to get to the less stable product, what if there's not as much of an activation barrier there. We'd like to think that it's generally the more stable product that's going to form, but kinetics does have an effect. If it takes so much more effort to make the more stable product, and if you gave each molecule just an equal chance to react, with a much smaller activation barrier for the unfavorable product, it might form faster. Over time, or if you have higher temperatures, the thermodynamic product would be the one that in the long run might form. But, especially if the reaction's not reversible, the first shot that you have, whatever product forms, it forms that's it. That decision of which product to form is actually often controlled, instead, by these activation barriers. There's what is known as kinetic versus thermodynamic control. Sometimes, even though you might want to make the more stable product, it might be too tough to.

That's exactly what you can do in these elimination reactions. If you use what is known as a hindered nucleophile, we talked about steric hindrance for S_N2 reactions, because there hindered substrates were bad. Hindered substrates encourage elimination reactions. We're going to talk about: when is S_N1 going to happen versus S_N2 versus $E1$ versus $E2$. The more hindrance that you have anywhere on the nucleophile or the substrate, the more elimination that's going to happen. But, when you already have an elimination, if your nucleophile is really sterically hindered, that's going to make it tougher for it to approach and remove a secondary hydrogen versus a less crowded primary position. If I did this exact same reaction using this kind of nucleophile – for short, it's called the t-butoxide ion. Alk-oxide – alkane oxide, the two words put together. The way that you can name different alkoxides is think of methane or methyl oxide: methoxide; ethoxide; propoxide; butoxide; so on and so forth. So t-butyl turns into t-butoxide. That is so sterically hindered that the major product formed is going to be this one. If a nucleophile itself is very sterically hindered, it can cause the formation of a less stable alkene due to kinetic effects. More hindrance around the nucleophile makes it tougher to remove more hindered hydrogens.

Let's step back and go over these six aspects of a reaction. First, the utility: alkyl halides (or sulfonates) are being converted into alkenes. Alkenes are the only functional group, for the moment, that we're going to see in these elimination reactions. In terms of reagents, if we're talking about the $E2$ reaction – you might anticipate that if I'm focusing on the two, you could guess that there might be an $E1$ reaction as well – the reagents need to be basic, strong nucleophiles. In terms of conditions, it's still going to be polar, aprotic solvents that work best, cause you don't want something interfering with the base. Mechanism, we have up above.

Stereochemistry. There's a couple of different stereochemical effects that occur in an $E2$ reaction. I want to describe just one example of that today. That's what happens with elimination in cyclic compounds. Let's think about the transition state for an $E2$ reaction. Let's say that we have a bromine that is at a tertiary position. Let's say that we have a hydrogen that's also at a tertiary position. Let's say that, therefore, I construct it such a way that only that hydrogen's going to be eliminated, so we're not worried about that alkyl group at all. What would the transition state look like? Remember the mechanism is that that hydrogen's being plucked off at the same time that the leaving group's being kicked off. Let's see what, if we just wanted to use dotted lines, that might look like. You have hydroxide, it's coming and pulling off a hydrogen. It's going to start the formation of an alkene and kick off the bromine. The transition state would look something kinda like this: bromine's coming off so I'll write it with a dotted bond. An alkene is starting to form, so I'll write that with a dotted bond. The hydrogen's coming off, and it's forming a bond with hydroxide.

What if we drew a partial SMOG. Think of it this way: if I have an sp^3 -hybridized orbital pointing to where originally the bromine was, and I also have an sp^3 -hybridized orbital pointing to where the hydrogen originally was. Notice that what's effectively going to happen is those sp^3 orbitals are going to be converted into p orbitals, converted into being a pi bond. A pi bond can only form, though, if these orbitals end up being parallel to each other. They are in this case, in a sense, because the hydrogen and bromine, they're both being written in the plane of the paper. I did that on purpose, because that's the only way, or one of the only ways, that you're going to get orbital overlap that would look like this, where they would be parallel and the pi bond would be easy to form. Another orientation that could work is if the hydrogen and bromine were pointed the same direction as each other. As this removal occurs, at least the orbitals involved – which start out sp^3 but become sp^2 – they'd still be parallel, in a sense, to each other.

Technically, this last case is the parallel case. The previous case is one that's known as antiparallel. But instead of using parallel and antiparallel, there's another term that's used: periplanar. Periplanar means they're going to be parallel to each other but separated by one position; periplanar you can think of as link parallel. This first case is antiperiplanar, which you can think of as parallel, but pointed 180° opposite. Eliminations can only occur if you do have this geometry between the hydrogen being pulled off and the leaving group. [actually synperiplanar] Eliminations can only occur if the hydrogen removed is synperiplanar or antiperiplanar to the leaving group.

Why does that matter? Let's say we had a case like the following: I put so many methyl groups on here so I could ensure that there's only one removable hydrogen that might react in an elimination reaction to get rid of that bromine. Notice, at the position to the left, I don't have any hydrogens there, so I can't eliminate from that position. But now look at this geometry: are the hydrogen and bromine antiperiplanar? If you were to make a rotamer diagram along this axis, you'd find out that, no, not in this position would be antiperiplanar. But, you can have a ring flip. If you did have a ring flip, you'd have this situation: [correct visualization] Now the hydrogen and bromine are antiperiplanar. Since, at room temperature at least, ring flips can occur quickly, that means elimination can occur for this compound.

But now what if I had this compound? Elimination can still occur from only one carbon, because the other carbon has two methyl groups on it, so there's no removable hydrogens there. [homework question][quiz review][lab reports]

6) Regiochemistry

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

Even though it's primary, this carbocation forms due to conjugation of the + with benzene.

1° allyl substrates are also reactive. vinyl → attached to the double bond

Vinyl substrates do not undergo Sn1 rxs because vinyl carbocations are not stable (orbitals with more s-character better tolerate – charges, but are worse at tolerating + charges).

In Sn2 rxns, vinyl substrates do not react because the pi electrons in the C=C bond repel the approaching nucleophile.

2) nucleophiles – For Sn1 rxn, poor nucleophiles – particularly non-basic nucleophiles – must be used, since the rxn will only occur the carbocation has time to form.

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

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

Eliminations – E2 – bimolecular elimination

More substituted alkenes are more thermodynamically stable.

Zaitsev's rule – In eliminations, the more heavily substituted alkene will be the most one to form.*

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

Identical to those from lecture 21A (11/18/11)