Lecture 22A • 11/23/11

Let's say that we have some kind of cyclohexane ring where we have a leaving group on one side of which there are no available hydrogens in order to be able to eliminate. Let's say, therefore, in this example we have on the other side one hydrogen that can be removed. We've covered the case already where we have a trans relationship between these two things on the ring, the leaving group and the hydrogen to be removed. This is the cis case. Let's try to make a chair structure for this molecule to see if we're going to have that parallel or antiparallel, or more correctly, [syn]periplanar or antiperiplanar configuration that would actually allow elimination to occur. I'll put the two methyl groups on the back carbon; coming clockwise around, we have bromine that's supposed to be pointed up, so it's going to end up occupying the axial position, and then hydrogen's pointing up – remember that if we had two things that were cis pointing the same direction, that if one was axial, the other one would automatically be equatorial, like what I've drawn here. This is just one possibility, though, so let's do the ring flip structure. In the ring flip, it's going to look like I've moved the methyl groups, but that's only because I need to visualize this is such a way where I still have the bromine and the hydrogen both pointed up. In terms of convenience, in terms of writing this where I still have the same slant for the chair structure, that's why it appears that I've moved things around to different carbons. Bromine is going to be up still, hydrogen is still down, then we have the hydrogen that's up and the methyl group that is down.

Can either of these give that [syn]periplanar or antiperiplanar configuration between the hydrogen and the leaving group? No. We could more clearly see that if we were to make Newmann projections. If we were to choose to look along this bond, where I'll put my virtual disc in the middle here to see what the configuration of the hydrogen and the bromine are; the Newmann projection would look like this. Those things that are in front are the things we write with bonds that go all the way to the center of the projection, and those things that are in back are those things that we write without bonds going all the way through. Bromine's at the top in the back, hydrogen is down and right, the rest of the ring is down and left; I'm going to write a little loop here to show that it's connecting to this upper-left point on the front carbon. On that front carbon, we have hydrogen and then the methyl group. Notice that there's only a 60° dihedral angle, so it is not parallel or antiparallel, so elimination's not possible in that case.

Now let's visualize a different bond. [model sets] If we're looking along that bond, we'll again have a configuration that looks like this. Let's see if we can figure out what is left/right/up/down. Looking at the back carbon, the methyl group is pointing out towards the left, [and] it's coming out relative to this viewpoint, so I'm going to put the methyl group down below here. The hydrogen is up above, and then we have the rest of the ring on the right side, which is going to loop around to the upper right, the rest of that ring. The hydrogen's going to be pointed down, and then bromine coming up to the upper left. In this case, we have another 60° angle; again it's not going to be in the correct configuration. In both cases, the leaving group (bromine) and the hydrogen that can be eliminated are neither synperiplanar or antiperiplanar, so elimination cannot occur. In the trans case, one of the two ring flip forms we did have antiperiplanar geometry. In this case, with it being syn, you can never get that geometry, so elimination just won't occur.

This is E2 so far that we've been talking about. Let's talk about E1, or unimolecular elimination. Any time that you have a basic nucleophile, it's going to encourage E2 elimination, because that nucleophile, being a base, is actively going to pull a hydrogen off. For an E1 reaction, we're going to use something that's a poor nucleophile that's going to allow the carbocation time to form, so it won't be able to come pull off a hydrogen on its own. We'll have this dissociation first, which is the same step as in an Sn1 reaction – which is, in fact, an important point. Since the SN1 and E1 reactions pass through exactly the same intermediate, there will always be some Sn1 that occurs with E1, and vice versa. Which one's going to happen really depends on a case-by-case basis. Often, if you have a large nucleophile that would have difficulty substituting, that might influence the product mixture and end up giving you a bit more elimination. But, [the] nucleophile is not directly related to the overall reaction rate; it is just the formation of this carbocation. Solvent or nucleophile may influence which one of these occurs, but you're always going to have both together. To finish off the mechanism, in an Sn1 reaction the nucleophile would come along and substitute at this point. The nucleophile comes and rips off a hydrogen that has to be on a carbon next door to where the carbocation is. Once that occurs, you're going to form the alkene. Why is it unimolecular? Because the formation of the carbocation is the rate-limiting step, and since only the substrate's involved in forming that carbocation, then that's why only that substrate's in the ring.

[flash cards] The six aspects of the reaction: utility – the synthetic utility is just like E2: it's to take an alkyl halide and turn it into an alkene. When I say alkyl halide, there's always going to be this footnote that we could be talking about sulfonates as well. As far as the types of reagents that are used? Like Sn1, this only works if you use weak, non-basic nucleophiles, cause if you have something that's basic, it's going to cause Sn2 or E2 instead. Conditions – polar, protic solvents, same again as Sn1. Mechanism, we have up above. In terms of stereochem, it's basically the same as the E2 reaction, where you've got to get the p orbital to form to be parallel to whichever hydrogen's going to be removed in order to make that pi bond. I want to get to regiochem, because for regiochem, [because of] the stability of different alkenes, more substituted alkenes are preferred. And, because this is a carbocation mechanism, carbocation rearrangement is technically possible; it's not in this example I gave because we already have a tertiary carbocation, it would not want to go from tertiary being a primary again.

Synthesis workshop

What I want to talk about are the different factors that are going to influence whether Sn1 occurs, Sn2, E1, or E2. Secondary's rough cause we could do all four reactions – if you have this particular secondary substrate and you have this kinda basic, but not really, nucleophile that's kinda strong but not, and it's got some steric hindrance on it but not a bunch, which of the four reactions will occur? I'm more worried about more clear-cut cases. Let me show you some of the specific cases I'm worried about. In fact, we can break these down, really, into two broad classifications. Really, it's eliminations that we're worried about; substitution can happen as long as you don't have something that's too strong or basic. The two broad cases we're worried about: if you've got a basic nucleophile, or if you have a non-basic nucleophile.

Let's handle the basic nucleophile first. This is our discussion of Sn2 vs Sn1 vs E2 vs E1. For a basic nucleophile, let's take a primary substrate. If we had a primary substrate and something basic like sodium hydroxide, the major product is going to be Sn2. Most primaries, Sn2 is more likely. E2 is not impossible, but E2 is much more likely the more hindered the system becomes. If you move up to a secondary substrate, even with a small molecule like sodium hydroxide, you're going to get, possibly, some substitution, but you're also going to get a non-zero quantity of the elimination product, because just moving up to a secondary is enough steric hindrance to start making elimination more likely, because it slows down substitution enough – more elimination due to more steric hindrance. This is the substrate becoming bulkier; what if the nucleophile itself had steric hindrance? Even if the reactive site is accessible, but we used a hindered nucleophile, like the t-butoxide ion, for a secondary, you've just pretty much guaranteed elimination. Tertiary, Sn2 is not possible, so if you throw anything basic at it, the only thing that's going to happen is elimination. This is all under the heading of using basic nucleophiles. I'll summarize the trends one more time: substitution happens the less steric hindrance that you have. Primary, substitution is usually the main product. Secondary, substitutions likely, but elimination's possible because you've got some steric hindrance. The more bulk that you put on the nucleophile, if it's basic, the more elimination's going to occur. For tertiary, since you can't have substitution, the only thing that's going to happen is elimination. Elimination can happen on primaries, but unless you use a really hindered nucleophile, substitution is easy enough that you get the substitution product.

If the basic nucleophile would be one category, that's going to mean that non-basic nucleophiles will be our other category. Let's do a primary/secondary/tertiary example again. Something like bromoethane, but now using water. You get a tiny, tiny, small quantity of this to form – not because of Sn1, because forming a primary carbocation just really is not favorable, but you'll get a slow Sn2, or, even more often, you might just not have any reaction. In a really technical sense, you'll get a slow reaction, but often, nothing will happen. As soon as we go to secondary, though, now the formation of a carbocation is possible. But, because you have the same intermediate to form the substitution product, you'll automatically get some elimination, so you'll get E1 and Sn1. Tertiary, much, much more rapid reaction; that's only because the carbocation is easier to form. As far as the product, you're still going to have a mix of substitution and elimination. The non-basic nucleophiles, especially weak non-basic nucleophiles, essentially it's Sn1 and E1, but not for primaries. I'm not going to try to catch you on the most obscure of cases; I want you to know these main trends. The type of reaction that occurs depends on the structure of the substrate and the basicity and bulkiness – which means size – of the nucleophile.

Fill-in-the-blank problems – one of the most common types of problems we're going to have on all exams from now on. Let me show you an example of one of these fill-in-the-blank problems. Let's say that I have a tosylate. I say it reacts with something to make this ether. What goes in the box? Ethanol. But why? What kind of reaction happened here? Why Sn1? Why does it have to be a weak nucleophile? Cause the leaving group has to leave, and yes, it's tertiary. It is substitution [that's going on]; we don't have elimination, so it has to be Sn1 or Sn2. It is a weak nucleophile, cause that's the only way we're going to get a tertiary substrate to react, which means it has to be an Sn1 reaction. This reaction is a substitution reaction on a tertiary substrate, which means a weak, non-basic nucleophile must be used. That means the answer is ethanol. It cannot be sodium ethoxide, because if it were, what reaction would you have instead? It would cause E2.

Let's do another example. We just saw one where the reagent is missing. Let's say we had something like this: alkyl halide reacts with sodium cyanide to make something. [What is the structure of the cyanide ion?] There's only two atoms there. Carbon has four valence electrons as a neutral atom, nitrogen five; this is a negatively charged ion, so 4 + 5 + 1 gives us 10 valence electrons total. The only way to do this without violating the octet rule is to make a triple bond and put a lone pair on both the carbon and nitrogen – which if we do, nitrogen has a formal charge of zero, carbon has a formal charge of negative one. Nitrogen's more electronegative than carbon is, but the only way it could get the negative charge is if we made a quadruple bond, which is not physically possible for nitrogen. That is the structure of cyanide. It is basic, and it is negatively charged, so it is a reasonably strong nucleophile. Which reaction is the one likely to occur? Sn2. Why? Because we have a primary substrate. It's not a bulky base, it's not huge, and it's not as basic even as hydroxide is, so it's Sn2 – we have a primary substrate and a basic but non-bulky nucleophile. If it's Sn2, then that means substitution. This is kinda an unusual way of writing it where, I'm writing the CN there, but the reason I did so is because this is a functional group known as a nitrile. This is actually a very sneaky reaction because it's one of the relatively few carbon-carbon bond-forming reactions. The majority of reactions that we learn are going to be to transform one functional group into another, but if you're going to make large molecules, you gotta have a way to be able to stitch carbons together. That's what we've done: the carbon happened to be in an ionic compound in this case, but it does make a carbon-carbon bond once the substitution occurs.

If you put a nitrile in extraordinarily basic or acidic conditions, you can convert that nitrile into a carboxylic acid, which then can be converted into esters, anhydrides, acyl halides, amides – several different functional groups. From there, you could get to practically any other functional group with a little bit of work. It's one way to introduce a new carbon-carbon bond into a compound. Here's out example of the product being missing.

Why don't we do one last problem where the substrate is missing. What kind of reaction's going to happen in this case? Elimination. It has to be E1 or E2 because we've got a double bond. Which one? Why E2? Bulky, basic nucleophile – we've got a negative charge on that oxygen and it's basic. This is E2 because we have an alkene produced and a basic, bulky nucleophile. There are actually three kinds of answers you could give. One would be like this: if we know that we make an alkene, we know that there had to have been a leaving group somewhere on this molecule, and it had to have been one of the two positions where this alkene is located, cause E2 doesn't have carbocation migration, so wherever the double bond formed, one of those positions used to have the leaving group. If I put it at this tertiary position, this is actually not the best answer, because if I reacted it even with sodium hydroxide, substitution's not possible so only elimination's going to occur, but we could get three different products: the one we want, plus, going the other direction along the ring, plus off on that methyl group as well. If I show only one product and the question says only one product forms, then this wouldn't be the right answer.

That means we're left with four other possibilities: [would not ask for multiple reactants; if there are multiple products that form, that I would ask for] four different diastereomers of having a methyl group and a bromine right next to each other. In two of these cases, the hydrogen ends up trans [to the leaving group], which means the reaction can occur, because antiperiplanar geometry is possible. For the other case, we draw the hydrogen in, we'll see that it is is cis [to the leaving group]. Cis means it's not going to happen because antiperiplanar geometry is not possible. Neither of these would be good choices; either the first one or the last one make the same molecule because you loose the stereocenter once elimination occurs, so either of those would have been acceptable answers.

Exam 2

Question 1 – First question is about different types of carbocations. You had a primary, a secondary, a tertiary, and you were told in the question that these different carbocations form at different rates, the tertiary forming more quickly than the secondary than the primary. I did indicate not to focus on kinetics, not to be thrown by the faster rate; what really I was getting at was the stability of those carbocations, but I couldn't use that word because that's part of the answer itself – that a tertiary versus a secondary versus a primary carbocation experiences more hyperconjugation. That hyperconjugation is what stabilizes and spreads out the positive charge and makes it easier to form. You were asked to do an appropriate SMOG. A general picture of a primary or tertiary carbocation is fine to do, but it is does not technically match the structure of molecule C. I'm going to write out the full SMOG for molecule C. The central carbon is sp2-hybridized. All the other carbons are sp3-hybridized. You do have the carbocation, you have a p orbital as well. Here are the three sp3-hybridized carbons that are directly attached to that carbocation. If you were drawing molecule C, here's that extra methyl group. Of course, there are hydrogens on those sp3-hybridized orbitals as well. You should go ahead and show the hyperconjugation interactions that are possible because that's kinda the point of the SMOG. One very minor point: some of you connecte the line from the carbocation coming to this ethyl group and connected all the way to the end. Hyperconjugation does not really occur more than one atom away, because you don't have the orbital overlap and it's not conjugation. The line from the carbocation should have only gone to those carbons that are immediately next door. Also, since the other atoms are sp3-hybridized, they don't have p orbitals left on them.

Second problem – this was about the allyl anion. The question says that the true structure of the molecule is not able to be shown by either one of these resonance structures. You're asked to draw a SMOG for the allyl anion, then you're asked to explain how and why neither resonance structure can reflect that true structure. The how part is what is it about that resonance structure that's not correct; the why is getting at delocalization. Neither of these structures is correct because the anion is not located just on one carbon; it is delocalized, it is spread out across the molecule, so it's being represented as being in only one place is incorrect. That place where you do have the negative charge would be sp3-hybridized, whereas the other two carbons are sp2[-hybridized], but in reality, all of them are sp2-hybridized. That's how it's in correct. Why it's incorrect? We don't have a writing system that can handle delocalized electrons, so we have to write it in this way so at least we can count electrons, but it's not the correct structure. Lewis dot structures or line structures cannot represent delocalized electrons. You were asked to draw a SMOG for this. All three carbons in this case are going to be sp2-hybridized, so it's going to look like this. There's hydrogens on each one of those atoms. We have conjugation occurring this time, not hyperconjugation. If you had drawn the SMOG based on one of the resonance structures, you missed part of the point of the question – that those resonance structures are not correct; you can't base your SMOG off of them.

Question 3 – this was the mechanism for the Sn1 and Sn2 reactions. You have reaction A, where you had a primary alkyl halide reacting with sodium hydroxide. Since it's primary and since you have hydroxide, there's going to be Sn2 that occurs. [we required to know in this limited example when Sn1 vs Sn2 occurs] The nucleophile attacks, kicks off the leaving group. Because it's Sn2, you're going to have inversion of configuration, so the hydroxide will not be pointed the same way as the leaving group was. For reaction B, we had a tertiary alkyl halide that reacted with water. Tertiary, weak nucleophile – means Sn1. First, the leaving group comes off. Arrows show the direction of atoms moving, they show the directions of electrons moving.

In this case, though, it happens to be the same thing: the pair of electrons in that bond comes to bromine because bromine is coming off. You make the carbocation, which water attacks, but since it's planar, it attacks from above and below, so you're going to get two different products out. I'll go ahead and write both products out, but as long as you acknowledge that there are two possible products [by saying "plus enantiomer"], [that's fine]. Here's our two intermediates. Positively-charged oxygen, so in both cases, a hydrogen will come off. This time, the arrow is opposite the direction the arrow's going because the pair on the bond falls back to oxygen, so we end up with two alcohols as our product[s].

Number 4 – you're asked to draw reaction coordinate diagrams. [tied grading to answer in question 3] Some of you have this idea that if there's water around, you'll have hydroxide around as well. That is technically true, but realize that, at room temperature for pure water, the concentration of hydroxide is 10^-7 molar – in other words, incredibly small. Effectively, there really isn't hydroxide in solution, as far as reacting in an organic reaction. Any time that you see water as a reagent, you cannot treat it as hydroxide. This particular version of Sn1 has three steps, so that means there needs to be three steps in your reaction coordinate diagram. Let's back up and look at the Sn2 diagram first. For A, since it's a one-step reaction, we're only going to have one hump on the curve of the reaction coordinate diagram, corresponding to it having only one transition state, one activation energy. There are no intermediates cause there's just one transition state, but we do have our reactants and products. The directions indicated that the reaction's exothermic, which implicit in that was the fact that you should have lower energy for the products than reactants. [scale should be delta H] For the Sn1 reaction, the full reaction has three steps, so we're going to have three transition states, so we're going to have three hills on our reaction coordinate diagram. You're not given enough information about the intermediates to know exactly which one was higher and lower in energy – other than the fact that the first step is the rate-limiting step. If that's the rate-limiting step, then that should have the highest activation energy. As long as the other two steps, the other two hills had lower activation energy, and as long as you made the product overall lower in energy, where the position of intermediate number two was was unimportant. There's our three stages – two intermediates, a product, there's our reactants. Again, the reaction will have three hills in it, with the first activation energy being the largest. Notice that the activation energies are draw starting from the reagent or intermediate that immediate precedes the transition state. You don't look at just the original reactant for all the different activation energies; it's just for that first step of the reaction. I'll label my transition states. These would be two complete reaction coordinate diagrams.

Question 5 – still refers back to question 3. You had these two different reactions, but it talks about their stereochemical outcomes. For reaction A, you end up with an optically active solution; for reaction B, you end up with an optically inactive solution. Why is that? For reaction A, it's because you only end up with one molecule, and it's chiral. It isn't enough to say that the molecule has stereocenters, because you can have something that's meso, for example – meso has stereocenters, but it's not chiral, so you do have to specifically refer to the fact that you have a chiral product, which is why you have optical activity. For solution B, though, the presumption was – because you weren't given any other information – that the reaction was racemic. In real life, Sn1 isn't always going to be racemic because the formation of ion pairs – but you're told it's optically inactive, so you'd assume that it was racemic. With that Sn1 mechanism, you should know you form both products, which are enantiomers of each other. Since you form both products and they're enantiomers of each other, then if you formed them in equal proportion, that's going to cause self-cancellation in the solution, which means, overall, the solution is optically inactive.

Nomenclature. First molecule was a deuterated cyclic alcohol. Building from the end of the name forward, this is cyclohexanol, which you don't need a number for it, because if you only have one of the most important functional groups on that cyclic molecule, it's automatically got the 1 position, so the end of this name will be cyclohexanol. There's three substituents – there's a deuterium and methyls. The d in deuterium comes before m in methyl, so we're going to have methyl being last. There's two of them, both at the 4 position, so that'll be 4,4-dimethyl. The deuterium itself is deutero. We have stereocenters on the molecule, so before any of this, we need to designate where we have R and S. Notice this is not a stereocenter up a the top of the molecule, because you have two of the same substituent, and since you have two of the same, it's not a stereocenter. Let's tackle the alcohol position first, since that's positon one. Oxygen's more important than carbon, so it's priority one. The ring is symmetric, other than the fact that we have the deuterium. Since deuterium's more important that hydrogen, the left part of the ring's more important than the right, so it looks like clockwise direction [of substituent priority], but the least important substituent is pointed out towards you, which means whatever we see we've gotta reverse, so that really is S. The other stereocenter, carbon with oxygen versus carbon; the ring's not symmetric form this point; at the first point of difference, you have an oxygen where on the other side, you don't. Carbon with oxygen, priority one; carbon without oxygen, priority two; deuterium, priority three; that is again S. The full name of this compound is (1S, 2S)-2-deutero-4,4-dimethylcyclohexanol.

The other compound, which was another alcohol. One common problem with this is how to handle the fact that you have three alcohols. It all has to do with the letter n that's in that name. For example, if we have a six-carbon alkane, that's going to be hexane. If you had a six-carbon compound with a double bond, that's hexene; the vowel changed from a to e, but the 'n' is still there. If it was a triple bond, it'd be hexyne. But that's for hydrocarbons; for other functional groups, it's what's after the 'n' that changes. You have, for example, hexanol for an alcohol, hexanal for an aldehyde, hexanone for a ketone, hexanoic acid. That 'n' is there in each of the cases. This is a triol. Because this have seven carbons in its longest chain, it's going to be heptanetriol. It's not heptatriol – the stem there, that 'n', stays there. The only time that anything changes related to it is whether you have an alkane, ene, or yne. End of the name: heptane-1,3,3-triol. You keep the 'e' in this case because 't' comes afterwards. You don't drop the 'n' when you're adding a functional group ending; you drop just the 'e'.

Propane, propanone, propanol, propanamine, propane thiol. The 'n' never disappears when you put a functional group end on it. Heptane-1,3,3-triol. We have three substituents again: we have an ethyl and a dimethyl, but the 'd' in the 'di' does not get alphabetized. So, even though it's two of them, you just look at the 'm' in methyl; that's higher that the 'e' in ethyl, so the methyls are going to go last. We have those in the 2 and the 4 position, so we'll have 2,4-dimethyl. We have the ethyl at the 5 position, and we again have stereocenters. The first stereocenter, position 2, we have carbon with two oxygens, carbon with one oxygen, and carbon with just hydrogens. It looks counterclockwise, but again the least important substituent is pointed out at you, so it's really R. The other stereocenter, we're also going to reverse whatever we see because the least important group is pointed out at you. We have carbon with oxygens, carbon with just carbons, and then carbon with just hydrogens. It looks clock, but it's reversed, so it's S. This is going to be: (2R, 4S)-5-ethyl-2,4-dimethylheptane-1,3,3-triol.

Last problem was about equilibrium. Let me write out the mechanism. Notice that sodium hydroxide does not show up anywhere in this equation. You have an acid that's present. If you were to somehow add sodium hydroxide to this, you would stop the reaction. Sodium hydroxide has nothing to do with this problem; it's all to do just with the ethanol that's there, or, even more importantly, the water that's produced. The problem first asks you to define what equilibrium is and then, using those definitions of equilibrium, describe a way that you could cause this reaction to go entire to completion. The three definitions were that there's no change in the concentration of reactants and products, that the reaction is at its lowest-energy point, and that the rates for the forward and reverse reactions are qual to each other. How could you make the reaction go forward? Remove the product as it is formed, because if you remove the product, you drop Q below K. You've changed the concentrations, but even more importantly, you have fewer products than you should, so Q is less than K, so the reaction is going to go forwards. If Q is less than K, that means the rate of the forward reaction is going to be greater than the reverse reaction; any time your disturb equilibrium, you're going to higher potential energy. Those are the three definitions being related to this methyl of forcing the reaction forward.

Sulfuric acid is a catalyst. The question also asks: why is it that a catalyst does not affect the balance of products and reactants. That's because it doesn't change the products and reactants. Hess's law says the change in energy for a chemical reaction only depends on those products and reactants, so if you're not changing them, you're not changing the overall reaction energy. Because of that, you're not changing equilibrium. It will change the rate of reaction, because you've given it a different pathway, you've given it a different activation energy. That activation energy has nothing to do with what the products and reactants are.

Let's go over the answers to the quiz. The problem on the quiz. What you had was an alkane, an alkyne, an alcohol, and a carboxylic acid. Those are the exact same examples that I had given addressing each of the three reasons why they are more acidic – why the alkyne, alcohol, and carboxylic acid are more acidic than the alkane. When comparing an alkane versus an alkyne, you have sp-hybridization on the alkyne versus sp3. When you put an anion in an sp-hybridized orbital, that's more favorable than putting it in an sp3. Hybridization is one of the effects that distinguishes alkynes from alkanes. The alcohol has an oxygen; that oxygen is electron-withdrawing, it's electronegative, so that pulls electron density away from the hydrogen to make it more acidic – that's the inductive effect. For the carboxylic acid, yes, you have a second oxygen, but even more importantly, once you dissociate the proton off that acid, you end up with something that's resonance stabilized – that's the resonance effect: if something makes the product more distributed in terms of its charge, it's more favorable to form.

Let's get to those pairs of [Sn1 and Sn2] reactions. First reaction was with a primary alkyl halide – a chiral primary alkyl halide – reacting with sodium hydroxide, versus a secondary alkyl halide reacting with sodium hydroxide. We only had the Sn1 and Sn2 reactions we were dealing with, so you needed to decide which one of the two was going to occur here. Which of the two could occur for either of these compounds? If we're looking at just the substrate, primary substrates can undergo which reactions? Just Sn2. What about secondary? Both Sn1 and Sn2, but what kind of nucleophile do we have here? Strong, and it's basic. Strong, basic nucleophile means that Sn2 is going to happen in both cases. We have a primary versus secondary substrate; in an Sn2 reaction, which one would therefore be more favorable? The primary, so the first reaction is the faster reaction. How could you answer this question if you weren't given concentrations and such? Since they weren't given as part of the question, the question wasn't trying to address concentration; it was focused just on this difference between substrates – exactly the same types of factors we have been discussing. There is going to be a big difference using a primary versus secondary substrate. This is Sn2 because we have primary and secondary, and we have, even more importantly, a strong, basic nucleophile. The primary's going to be faster than the secondary, due to the lack of steric hinderance. The product is going to be an alcohol with inversion of configuration.

The second problem – similar type of thing. We have a secondary again and a primary again. What kind of nucleophile do we have this time? We have a weak, non-basic nucleophile, so what kind of reaction should occur? Sn1, but can Sn1 happen with primaries? Not really, maybe the tiniest trace could occur if you let the solution sit around for forever, but, essentially, no. Really, only the first reaction's going to happen in this case. Sn1 because we have a weak, non-basic nucleophile. The secondary is better than the primary due to hyperconjugation. The product – you'll again get alcohols, but you'll get alcohols plural, because you're going to have substitution from either side of the carbocation.

The next pair of reactions. This is the only one you might be able to call a trick question, but this is really getting back to mechanism. You have the same tertiary substrate and you have two different nucleophiles. What kind of nucleophiles are these, though? Weak nucleophiles; they're non-ionic. Given the substrate, what's the only reaction that's possible. You might have been tempted to look at this and say sulfur is squishier, more polarizable than oxygen, but does the nucleophile have an effect on the rate of an Sn1 reaction? No.

Backing up just for a moment, if you look at those two reaction coordinate diagrams, part of the question was: why is it that, in reaction A, both the concentration of the substrate and the nucleophile matter for reaction rate, whereas in reaction B, only the concentration of the substrate matters? Because in reaction A, you only have one reaction step, so both molecules are automatically involved in that one reaction step, so they both are in the rate-limiting step, so they're both in the rate law. But in the second reaction, that formation of the carbocation is this step with the largest activation barrier, so it is the rate-limiting step, and there is no other reagent that is reacting at that time, and so only the substrate is going to have an effect on the rate of the reaction.

Coming back to this problem, only the substrate's going to have an effect on the rate of the reaction. Since you have the same substrate, that means they both go at the same rate. As far as the product, I'll just write the first one as an example. For the other one, it would be sulfur instead of oxygen. Sn1, weak nucleophile, tertiary substrate. They're the same rate because only the substrate is in the rate law.

The next one. This is where the identity of the nucleophile comes up, cause we've got a primary substrate, and we've got basic nucleophiles again, so that means Sn2. Since it's Sn2, because it's primary, the nucleophile does matter in this case, so now the fact that sulfur is bigger and squishier, since it's more polarizable, it forms a bond more easily to kick off that leaving group, sulfur ends up being the better nucleophile. It turns out that the benefit of polarizability for halogens is not as strong a determining factor for its reactivity as the basicity of the halogens. For this case, oxygen versus sulfur, polarizability is the more important factor. It's the second reaction that goes more quickly, and the product in this case would be a thiol. Sulfur, better nucleophile due to polarizability.

Last reaction. A sulfonate – specifically a mesylate – reacting with sodium hydroxide, versus an alkyl fluoride reacting with sodium hydroxide. Again, this is an Sn2 reaction because we have primary substrates and a strong, basic nucleophile. It's going to be a sulfonate that reacts more quickly – which would be true regardless of whether it's Sn1 or Sn2, because for both reactions, it is the structure of the substrate that matters. Even if you didn't remember pKa values, you should have remember that fluoride, out of the halogens, is a poor leaving group, because fluoride is basic, where the other three halogens are not. There are some cases where it can be a leaving group, but fluorine has really messy reactivity, so it is a poor leaving group to use. Sulfonates, though, are conjugate bases of really strong acids, so they're excellent leaving groups. It's going to be the first reaction that's quicker, because sulfonates are good leaving groups. Fluoride is basic, so it's a poor leaving group. Since it's sodium hydroxide that was reacting, our product is going to be an alcohol.

_____

In both cases the leaving group (Br) and the hydrogen that can be eliminated are neither synperiplanar nor antiperiplanar, so elimination cannot occur.
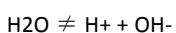
E1 – Unimolecular elimination

Since the Sn1 + E1 reactions pass through exactly the same intermediate, there will always be some Sn1 that occurs with E1 and vice versa.

1. utility: alkyl halide -> alkene
2. reagents: weak, non-basic nucleophiles
3. conditions: polar, protic solvents
4. sterochem
6. regiochem: more substituted alkenes tend to form; carbocation rearrangement is possible.
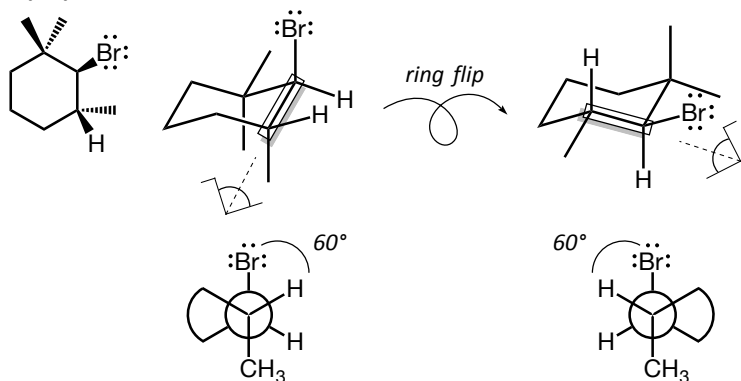
Sn2 vs Sn1 vs E2 vs E1

The type of reaction that occurs depends on the structure of the substrate and the basicity and bulkiness of the nucleophile. (size)

This reaction is a substitution rxn on a 3° substrate, which means a weak, non-basic nucleophile must be used. Cannot be ethoxide; would cause E2
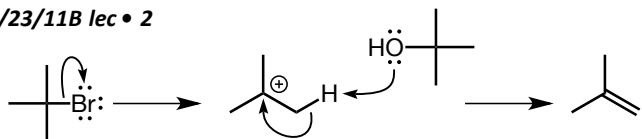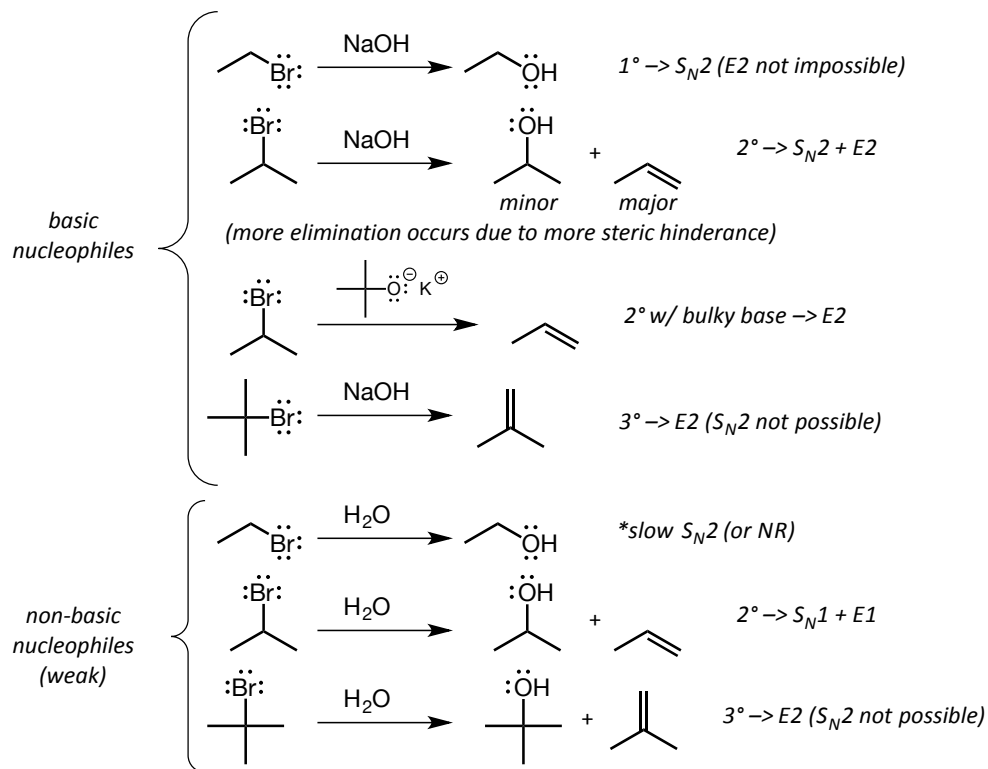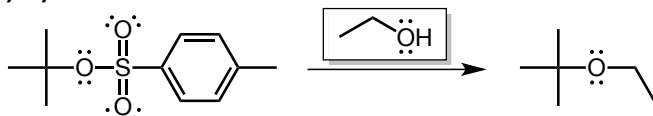
$H2O \neq H+ + OH-$

Structures

ring flip

60°   60°

CH₃   CH₃

NaOH → 1° –> S_N2 (E2 not impossible)

NaOH → minor + major   2° –> S_N2 + E2

(more elimination occurs due to more steric hinderance)

→ 2° w/ bulky base –> E2

NaOH → 3° –> E2 (S_N2 not possible)

basic nucleophiles

H₂O → *slow S_N2 (or NR)*

H₂O → + 2° –> S_N1 + E1

H₂O → + 3° –> E2 (S_N2 not possible)

non-basic nucleophiles (weak)

NaCN

⊖:C≡N:

nitrile

Sn2 (1° substrate, basic non-bulky nuclophile)

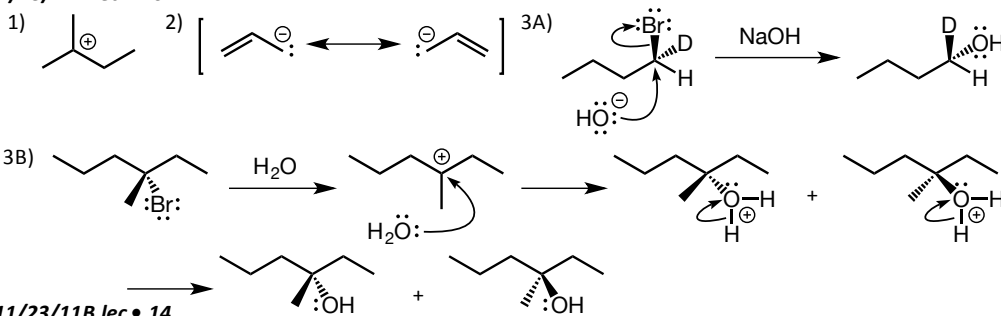*E2 (alkene produced; basic, bulky nuclophile)*

340

NaOH

+ +
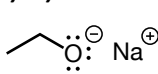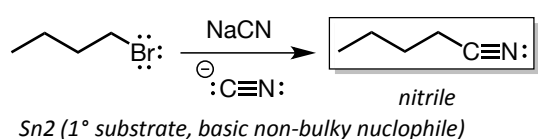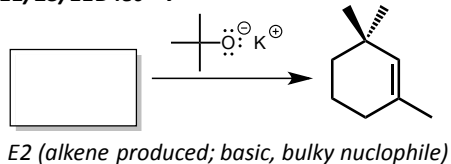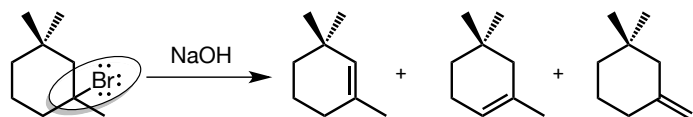
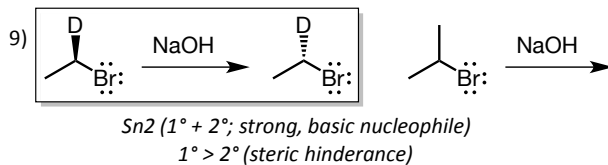*not the ideal loation for the leaving group since multiple products would form*

cis
(antiperiplanar geometry
is not possible)

trans
(antiperiplanar geometry
is possible)

6A)

D
:ÖH

(1*S*, 2*S*)-2-deutero-4,4-dimethylcyclohexanol

6B)

ÖH
ÖH

(2*R*, 4*S*)-5-ethyl-2,4-dimethylheptane-1,3,3-triol

Ö   ÖH   NH$_2$ SH

2-propanone   1-propanol   1-propanamine   1-propanethiol

1)   2)   3A)   :Br:
                                              D   NaOH   D   ÖH
                                              H   H

HÖ:⊖

3B)   H$_2$O   ⊕   O—H   +   O—H
     :Br: H   H
                H$_2$Ö:

                  :ÖH   +   :ÖH

9)   D   D
            NaOH   NaOH
     Br: Br: Br:

Sn2 (1° + 2°; strong, basic nucleophile)
1° > 2° (steric hinderance)

7) :Ö: H$_2$SO$_4$:Ö:
        ÖH$_2$ +   ÖH   Ö   + H$_2$O

        Br: H$_2$O

            H$_2$O   :ÖH   +   :ÖH
     :Br:

Sn1 (weak, non-basic nucleophile)
2° > 1° (hyperconjugation)

    Br: ÖH   O   Br: SH

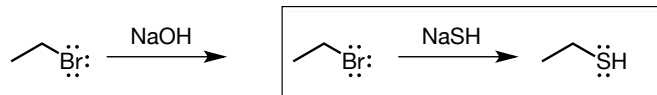*Sn1 (weak nucleophile, 3° substrate)*
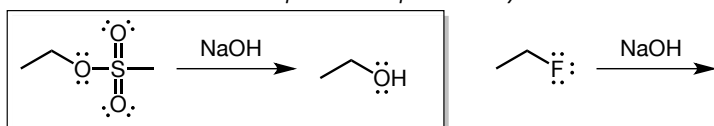*same rate (only substrate is in rate law)*

            NaOH   NaSH
     Br: Br: SH

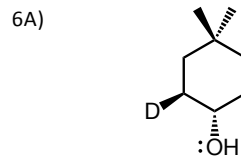*Sn2 (1°; basic, strong nucleophiles)*
S better nucleophile due to polarizability

        Ö   NaOH
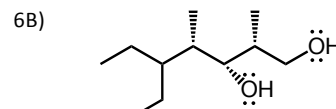   O—S—   ÖH   F: NaOH
        Ö

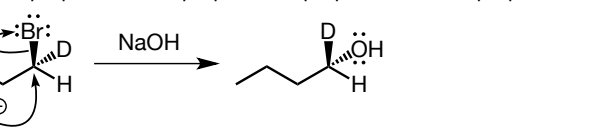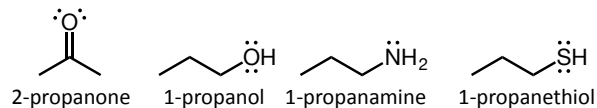*Sn2 (1°; basic, strong nucleophile)*
sulfonates good leaving groups (F- is basic)