

Lab 7A • 10/19/11

Nucleophilic substitution

To begin this discussion of nucleophilic substitution, let's look at this example. We'll take bromomethane and sodium hydroxide.

Naming of alkyl halides

There is the systematic way to name alkyl halides and then the common nomenclature method. In the systematic, we do treat the bromine as a substituent, so we call it bromo, so we can call this bromomethane. Notice that there's no '1' used because there is only one carbon in methane, so why number it if it's obvious? That is a small facet of the rules that we already saw when we named ethanol. Ethanol, because whichever carbon you put the oxygen automatically because carbon 1, and it's not possible to have ethan-2-ol, that's why we leave the number out in that case as well. Bromomethane, related to that is the general name for this kind of functional group, which would be haloalkane, halo- being the substituent style name and then tacking it on to an alkane; this is for systematic nomenclature.

The other possibility is that we treat the bromide as the important feature of the molecule. For example, we can call it methyl bromide, methyl being the substituent name, bromide now focusing on the halogen. The general term for this class of compounds using the common nomenclature system would then be alkyl halides. Although I do prefer the systematic names, even my own self I'll still say things like alkyl halides instead of haloalkanes, or I might say t-butylbromide, because it's a little bit quicker than saying 2-bromo-2-methylpropane. You need to be familiar with both systems.

First, where would you say that the center of reactivity is on bromomethane? If anything is going to react, if any portion of that molecule is going to react, where's it going to be most likely? Bromine's going to be involved, but it's really the carbon that's going to end up being attacked in this case. Why do you think a molecule like this would even be reactive? What structural property of this molecule might make it attractive to other molecules to attack? Why would another molecule even approach this molecule, other than the fact that things move around in solution? What might draw hydroxide to that carbon? Bromine is a halogen, halogens tend to be electronegative, it's going to pull electron density away from the carbon and make the carbon slightly positively charged. We have this fully negatively-charged hydroxide that, just on the basis of charge alone, then, is attracted towards that carbon. In fact, there's two terms that we use in mechanisms: one is electrophile – which literally means electron-loving, so something that likes electrons, it's seeking out negative charge. The opposite is nucleophile, which that term comes from the fact that nuclei are positively charged; nucleophile means something that seeks positive charge.

In this reaction, the hydroxide would qualify as the nucleophile. The alkyl halide, haloalkane, is the electrophile. What does happen in this reaction is hydroxide will attack the carbon center. Remember that the tail of the arrow shows where the electrons come from and the head of the arrow shows electrons go to. This means that a pair of electrons come from the hydroxide and attack and make a bond with carbon. Except that carbon is tetravalent; it only has a maximum of four connections to it, so something has to give. What makes more sense to give? The bromine, since it's already pulling electron density away from the carbon. We'll end up with an alcohol – methanol – as the product, plus, we'll have this bromide ion that's just floating around in solution. We'll see later on that this is called a substitution reaction, because we're taking that bromine and replacing it with something else. This also, in general chemistry terminology, would be a single-replacement reaction; in an organic sense, we call it a substitution reaction.

Let's look at a series of alkyl halides to see how the reaction may differ in rate from one compound to the next. We already looked at bromomethane. Let's compare it with bromoethyl, 2-bromopropane or isopropyl bromide, and 2-bromo-2-methylpropane or t-butylbromide. In that last compound, what kind of carbon do we have at the point where bromine attaches? A tertiary carbon. What do we have in the next compound over, the isopropyl bromide? A secondary carbon. And then the next compound? Primary? Then what would we name the methyl bromide? We don't have a term for it because there aren't any carbons attached. Numbering-wise, if I was following this scheme, I would say it's 0°, but you really just call it a methyl group. So you could say methyl halide, primary halide, secondary halide, or tertiary halide. It turns out that there's a vast difference between the reactivity of these different compounds. The order of reactivity is: the methyl halides are the most reactive, the most quickly-reacting of the compounds, followed by the primaries, followed by the secondaries, and a far-distant finish for the tertiaries. In fact, tertiaries are so slow, they're pretty much not reactive.

Based on the reaction mechanism, can you come up with a reason why this behavior might be true? Steric hindrance. If you look at the t-butyl bromide, it's really deceptive how we have that drawn on paper, because it looks like such a small stick figure. But recognize that each of those three methyl groups has three hydrogens on it, so there's nine hydrogens plus those three carbons that kinda form a shield around that whole molecule. Notice that the mechanism is one in which the hydroxide is attacking at the same time the bromide is coming off, so the hydroxide has to be able to get into and get its way towards that reactive center. If there's too much stuff blocking its route, the reaction just won't occur. This is the effect of steric hindrance.

So, methyl and primary alkyl halides are much more reactive in this particular mechanism because they have less steric hindrance around the reactive site. This is our first example of seeing a relationship between structure and reactivity. When we have something like the t-butyl group, where there's so much steric hindrance that the hydroxide can't come in, that's why it doesn't react. The methyl group, there's practically nothing there, so hydroxide has an easy time attacking, so that's why the rate is so much greater.

One other aspect of this that's important. R or S? S. Why? Hydrogen is in the back, so whatever we see, we report. In other words, we don't have to reverse it. Chlorine is the most important substituent; why? The highest atomic number. In terms of atomic number, we have chlorine, carbon, and two different kinds of hydrogens. Chlorine is the higher atomic number, so it's priority 1; carbon is priority 2; between the two different types of hydrogens, how do we decide between them, between hydrogen itself and deuterium? Mass number, that's the sub rule. For first it's atomic number, then when you get to a tie, it's mass number. So deuterium, higher mass number than the hydrogen, which is unwritten in the back, since this is all oriented the correct way, we can read around the circle, figure out it's S. If I wanted to name this compound, if we only have one stereocenter on the molecule, you don't need a number for the stereocenter. In other words, I could just start out with (S), without a number, because a chemist who writes this structure would recognize there's only one stereocenter, so you'd know which way to write it. (S), then we have a chloro- substituent and a deutero-, the substituent name for deuterium. What number would be given to the substituent position? 1. Deuterium is just a deuterium, so this is the end of the carbon chain, so this position is itself position 1. This compound is (S)-1-chloro-1-deuterobutane.

The reaction between hydroxide and this alkyl halide, it's a simultaneous reaction in that at the same time the hydroxide's coming in, the carbon-chlorine bond breaks. That means there's a particular geometry that occurs as the reaction proceeds. In fact, to get really technical, the hydroxide put electrons in the antibond of the carbon-chlorine bond. What does that mean? If you had a carbon-chlorine bond and now you put electrons in that same antibond, the bond's going to break. That's why the carbon-chlorine bond goes away. But, because it's going away, the oxygen's there and now forms a bond with carbon. But because of the specific arrangement, the geometrical arrangement – something is coming in at the same time that something else is going out – that means that the product you end up with will have a reversed configuration. This is called inversion of configuration. The geometry at the stereocenter is inverted during the reaction. Why do we care about this? You can end up in situations where you'll have enantiomers, mirror-image molecules, where one form might be beneficial and one form might be harmful, so it matters entirely whether or not that wedge or dash does change or not during a chemical reaction. This is our first chance to connect a mechanism to what kind of stereocenter we're going to end up with.

There's one side detail: regiochemistry. Regiochemistry refers to whether a reaction takes place at just one reaction site, or whether you might get the possibility of forming different structural isomers; in other words, whether the reaction might occur at different places along the molecule. In this example, you can see the nucleophile, the thing that wants positive charge, is substituting in exactly the same place every time, where the halogen is, where that delta positive is, so it has very regular, predictable regiochemistry. Regiochemistry refers to whether a reaction occurs at only one site or at multiple sites.

In this reaction, something is getting substituted by a nucleophile, so it's called nucleophilic substitution. But more specifically, the version of the reaction I've shown you so far is referred to as bimolecular nucleophilic substitution, or S_N2 for short: S for substitution; n which is written as a subscript but capital, that stands for nucleophilic, and then the 2, bimolecular. Bimolecular nucleophilic substitution is the name of the reaction I've been showing you. What does the term bimolecular mean? It has to do with a rate law. What's the general form of a rate law? R, and then there's some concentrations that get thrown in there, then there's this k thing, the rate constant. What determines which concentrations get put into this expression? What, in terms of a chemical reaction, establishes which compounds go into the rate law? You can have multiple reagents that change concentration [during reaction] but don't change the rate of a reaction. The rate-limiting step.

This is a reaction coordinate diagram, which monitors the energy of a reaction as it progresses from reactants to products. There are several important features that we often point out on one of these reaction coordinate diagrams, one of which is activation energy, which is related to this concept: you can have a match, but no matter how bad a mood you might be in, you can stare at that match all day long, but it's not likely to light all by itself (or if it does, you're super-special). Barring that, you've got to strike it. You've gotta add friction, which adds kinetic energy, which adds the energy necessary to get molecules up over this hump. Kinda like an amusement park ride: once you get up to the top, then it's pretty much a downhill ride – you hope – afterwards. This tallest, toughest part of the reaction, in between reactants and products, it's called a transition state. The transition state is the highest-energy moment as you go transitioning from reactants to products.

Notice that you might have multiple individual steps in a reaction. This particular diagram is not representative of the reaction I've been showing you so far. What I'm showing you is an example of something that has multiple transition states, multiple tough moments. But, one of these activation energies is a lot larger than the others. You go from the very beginning of the reaction up to the first transition state, there's a lot of energy; you go from this intermediate to the next transition state, it's just a little bit of energy. In general, the rate of a reaction is controlled by the step that has the largest activation energy. That step is known as the rate-limiting step. In a reaction, you might have multiple steps. They'll each have their own activation energies.

The one with the largest activation energy tends to control the rate of the reaction. Why? Because the rate constant that we throw in, there's a formula for it that involves activation energy as one of the prime variables. In a purely mathematical analysis, we increase E_a , k goes down; the rate of reaction goes down. That's an [unsatisfying] way to argue this, because all I'm doing is using the equation. Physically what's going on? This diagram represents the fact that, at any given temperature, you're going to have a distribution of energies of molecules. For example, at room temperature, water evaporates, even though the boiling point of water is 100 °C. That's because some of the molecules are moving fast enough that they can escape. The same thing happens in a chemical reaction. If you establish an activation energy, that means a fraction of molecules are going to have that amount of energy and can react, while other won't have enough energy. If you raise the activation barrier, you lower the number of molecules that have enough energy, which is why the largest activation energy controls the rate of reaction.

So what does bimolecular mean? It means there's two molecules involved in the rate-limiting step. How do we know this reaction is classified as bimolecular? Do you see any 1's or 2's indicating the order that these arrows occur in? No. Is there any indication from the way that I've drawn the mechanism that there's any kind of timing involved? No. That's on purpose, because when you write multiple arrows in one diagram, it means they're all happening at the same time, what's called a concerted reaction. Because both of the molecules are involved at the same time, because both the nucleophile and the substrate – the target organic molecule that's getting transformed this reaction – are both involved simultaneously in the rate-limiting step, that's why it's called a bimolecular nucleophilic substitution.

This is only half the story. Because, if I take t-butyl bromide and react it with bromide in water, under certain conditions.... In chemistry, what does a triangle pointing up refer to? Heat. So this alkyl halide, if it's heated in the presence of water, we're going to make an alcohol. As a separate reaction, if I take the same methyl bromide that we saw before, but instead of hydroxide, I react it with water and heat, nothing happens. NR is a common abbreviation for no reaction. We saw earlier how hydroxide reacts much better with things like methyl bromide, because there's no that much steric hinderance to get in the way of the hydroxide, and t-butyl bromide would be a terrible molecule to use with hydroxide, because hydroxide can't get to the carbon center. But this is not hydroxide, this is water. Why would t-butyl bromide be more reactive?

What if, when we use water, the reaction does not occur all at once? Think of what the story was with hydroxide: hydroxide was forcing its way into the molecule, attacking that carbon position, then forcing the bromine to come off. Is water more or less nucleophilic than hydroxide? Which one wants positive charge worse: the negatively-charged hydroxide, or the neutral water? Negatively-charge. We have negative that wants positive; if you had neutral, it could care less. So this is not as good of a nucleophile we're using, water. Then what's happening in this reaction? What if the bromine could come off all by itself for some reason. What is the shorthand term that we use to describe an organic molecule with a positive charge on the carbon? Carbocation. Specifically, this is a tertiary carbocation. What if I told you that tertiary carbocations form much more rapidly than the methyl or primary carbocations? That might explain this reaction, because notice it's the methyl bromide that doesn't want to react. Can you think of a reason the tertiary carbocation might be more favorable and more able to form? Hyperconjugation.

It doesn't make much sense to show you what hyperconjugation is before I should you conjugation.

I've just drawn up two structures that are used to represent what's referred to as the allyl cation. Allyl is another common name, referring to a double bond with a single bond on the other side and something else on that single-bonded carbon. Since we have a cation there, that's why it's called an allyl cation. Common name if we put an alcohol on it would be allyl alcohol. {Benzyl, phenyl, and crotyl} Which of the two structures for the allyl carbocation is correct? It might be taken as a trick question since the two structures are identical. So the correct answer is neither. Neither of these represents the structure of the molecule, because in real life, there is no double bond and single bond; they're both about the same length as a one-and-a-half bond. There's no difference between the three different carbons; they're equally distant from each other, the two on the left and the two on the right. How is that possible? What if we drew a SMOG.

{warning of prominence of SMOGs on future exams}

What is the hybridization of the carbon where the positive charge is located? {warning that knowing how to determine hybridization is critical} There are two unwritten – and only two unwritten – hydrogens on that position. If you look back at the example molecules when we did SMOGs, remember the methyl cation, it only had three bonds two it, so carbon is positively-charged if you only have three bonds to it and no other electrons attached. Since we only had three bonds, we need three unique ways that those hybrid orbitals are going to point. Three unique hybrids means three atomic orbitals, which is why it's sp^2 . What about either of the carbons in the double bond? They're also sp^2 , because there's only three single bonds on either of the carbons. Remember that the pi bond doesn't count for hybridization. If they're all sp^2 , let's draw a SMOG for this structure.

Here's the question: which pair of p orbitals do I connect? That's the same problem as how do I draw the structure. If the two p orbitals on the lefthand side are close enough to overlap, so are the p orbitals on the right.

There isn't just one overlap that occurs; you do not have a pi bond, you have a pi system. This is resonance. It's not that you have two molecules; it's not that you used multiple structures to represent it. Well, yes we do, and the reason is you can't write that bond using normal line structures. Some people try to; they try to do things like this, but it's a horrible idea, because you can't count electrons that way. One major point of writing structures down is to count where electrons go. Since the electrons aren't just in one place, that's why you can't write just one structure. That's resonance. This is also conjugation. Conjugation is where you have a bonding interaction due to the overlap of orbitals on more than two atoms. In this allyl system, we would say that the p orbitals are conjugated with each other. It's not just two orbitals making a pi bond, it's three making something special.

Why didn't I connect the line between the first and the third? Because they don't make a triangle; they're not close enough. If we got rid of these hydrogens and we pulled the molecule around and made a cyclopropene type of molecule, and then each one had a p orbital, they would all be conjugated with each other; the first and the third would then overlap. Because they're not close enough because there's not a bond between them, that's why there's no overlap there. In the case of the diradical, p orbitals were perpendicular to each other, but in this case, they do overlap. They are not perpendicular in this molecule, they are parallel, which is why all three overlap. There is no double bond in this molecule. This is a fake structure. This is where we try to represent this molecule on paper, but we can't. That's why we need resonance structures. You can't look at them and say where's the double bond; there is no double bond. It's just the way that we write it on paper. There's p orbitals on all three positions; they'll overlap simultaneously. So, you don't have a pi bond, where you have just a bonding orbital and an antibonding orbital; you have, in this case, three orbitals: bonding, non-bonding, and antibonding.

Let's go back to hyperconjugation. Why is it that this tertiary alkyl halide can form a carbocation at all, while it appears not to happen for bromomethane? Let's draw a SMOG of this tertiary carbocation.

There are two cases in which the p orbitals will be perpendicular to each other: one is for vicinal diradicals. Any time you have a radical on atoms that are next to each other, the only way to keep them as radicals is if the p orbitals are perpendicular. The other case is for cumenes, which is when you have a double bond connected to a double bond. What is the hybridization of the central carbon of that molecule? sp, not sp². You can't automatically say: double bond, sp²; normally you would be right, but this is the one time you'd be wrong. Because there's only two atoms attached to the central carbon, that's why it's only sp hybridization. That means you have one p orbital that's pointed in the plane of the paper and you have another p orbital that's pointed out at you. The one that's in the plane of the paper makes a double bond with one atom on one side, the other p orbital that's perpendicular makes another pi bond with the other atom on the other side, and the two do not overlap.

We're working on a SMOG for this carbocation. The central carbon, what is its hybridization? sp². What about the three methyl groups? sp³. Here's the point: a single bond on a carbon next to the p orbital can occasionally have just the right geometry where there's some small amount of overlap that occurs. This is already a sigma bond, the bond between carbon and hydrogen. This is an empty p orbital, a non-bonding orbital. This is not a proper bonding overlap that's being shown here. But, it is an overlap. What will happen is that some electron density from the bond will be funneled and smear over to where the p orbital is. That means that you've taken the positive charge which used to reside just on that central carbon and spread it out a little bit, spread the burden of tolerating that positive charge out across the molecule. The more you could dissipate that positive charge to spread it out, the more stable that a molecule tends to be. In this case, hyperconjugation can occur with not just one neighbor, but three. Remember that all of these single bonds are going to be rotating constantly, so it's not that you have three interactions simultaneously all of the time, it's that you have three neighbors with which these hyperconjugation interactions are possible.

Hyperconjugation is a non-bonding orbital interaction, which indirectly is going to involve more than two atoms as well. We have the p orbital on the second carbon and we have the sigma bond on the carbon-hydrogen bond next door. Let's go back and look at the methyl group, to explain why methyl bromide won't react. We've already drawn a picture for CH₃⁺, but let's take a look at it. Notice that there's a 90° angle between the carbon-hydrogen bonds and the p orbital. The bonds going from the carbon with the p orbital are in the wrong geometry to be able to overlap with the p orbital itself. That means that there's no hyperconjugation. In a tertiary, there's three neighbors that have hyperconjugation; secondary, only two; primary, only one. This explains the order of reactivity in this kind of substitution reaction. If we look at the same types of substrates that we had from the previous reaction, the same compounds are now going to have reversed relative rates of reaction. Why? Because the difficult part of the reaction, which is the formation of the carbocation, happens more easily with tertiary and secondary substrates because the carbocation that forms is more stabilized by hyperconjugation. In this type of reaction, tertiary alkyl halides are much more reactive, than methyl or primary alkyl halides because the carbocation formed during reaction is more stable. Methyl and primary alkyl halides are, for most purposes, are non-reactive by this reaction mechanism.

Let me write the full mechanism out. In that reaction mechanism, the carbon-halogen bond breaks. Why? Because there's enough energy around to get over the activation barrier to break that bond. Once you do make the carbocation, it's not as bad as if you didn't have a tertiary alkyl halide. Once you form the carbocation, now water can come in for the attack. What's the geometry of that carbocation? It's sp²-hybridized, but there are no lone pairs, so it's trigonal planar. Planar, which means, if the molecule is entirely symmetric, then is there going to be any preference for the [water] attacking from the top or bottom?

It'd be a 50/50 shot, everything else being equal. Well, the molecule is pretty darn symmetric. There is an effect that goes on in solution that may make this not quite be so even. Water attacks from two different positions. In this particular case, even though attack from two directions is possible, there's no stereocenter, so there's no need to worry about attack, at least on paper. Notice that this is not a final product yet, because once water attacks, water used to be neutral, the oxygen in water used to be neutral, but because it formed a new bond, it's now positively charged. A little step is that hydrogen comes off and you're left with an alcohol. That's the full mechanism.

This is called unimolecular nucleophilic substitution, or S_N1 . Why is it called unimolecular? How many steps are there in this reaction? Three. Each forward arrow represents a distinct step. Out of these three steps, which one would you guess would be the most difficult of them? Why the first one? The activation energy would be largest. Why? What's happening in steps 1 and 3 that's not happening in step 2? Bond-breaking, and bond-breaking takes energy. Bond-forming releases energy. Out of the three steps, step two is going to be the most favorable. Between the first and last step, you could look at the oxygen and say that oxygen doesn't like to be positively-charged, it's electronegative, so getting rid of that positive charge might be a good thing, and it is. Taking a neutral molecule and trying to break it apart, that's tough. The first step is the toughest step in the reaction. How many molecules are involved in that rate-limiting step? Only one, that's why it's called unimolecular. Only one molecule is involved in the rate-limiting step, which is the formation of the carbocation. That has a real practical consequence, which is that if you're doing this reaction, and you throw in a whole bunch of water or a little bit of water, it doesn't really matter, because the quantity of water won't change the rate of reaction, because all that matters is whether you form the carbocation or not. That's why it's called nucleomolecular nucleophilic substitution.

Let's come back and address that stereochemistry question. If I started out with a secondary alkyl halide and reacted it with water and heat.... is this R or S? R, because chlorine is priority one, priority for two for something that's longer than a methyl group. It's not automatically the longer chain that wins, but since we're just comparing carbon, then the thing with two carbons in a chain versus one in the chain, the two is going to win. Yes, it's R. But because when you form the carbocation, the very first step is to make a planar intermediate, then when water attacks, unlike what we saw above, we now will form two distinct products. It is critical to know that multiple products form because stereochemistry is important. {commentary of place of stereochemistry in organic texts} We have these two intermediates that form; they're enantiomers of each other. There is one more step where the hydrogen comes off and you make a racemic mixture of alcohols.

And that is nucleophilic substitution.

{lab lecture}

crotyl, benzyl

For S_N2 , it is a mixture of sodium iodide in acetone. Acetone is a fairly polar organic compound: polar enough that some small quantity of sodium iodide is soluble in acetone. Turn out, though, that sodium chloride, sodium bromide are not so soluble. So if you have a reaction where iodide can substitute – let me show you an example reaction mechanism. I'll use one of the compounds that you're going to use in your experiment, because we have discussed how primary alkyl halides should undergo S_N2 . So iodide would kick off the bromide, you'll form an alkyl iodide as a product, but because bromide is less soluble in acetone than iodide, with sodium present, the sodium bromide should form a precipitate.

{description of observation of successful reaction}

Silver nitrate in ethanol. Why does this encourage S_N1 conditions? Because in S_N1 , the halogen comes off first. If you have a free halogen with silver present – halogens are normally soluble in aqueous solutions, unless there's silver, mercury, or lead present. We have silver present, so if the halogen comes off, it's going to precipitate. Here's an example mechanism for what happens in the S_N1 case: the halogen comes off, you form a carbocation, you'll have a halogen that will end up precipitating, and then there's ethanol left over. Ethanol may be the solvent, but it's also the reactant; for S_N1 reactions, the reactant is often made the solvent so you can flood the reaction with it. After than bond forms, we'll initially have a positively-charged species. The positively-charged oxygen is not favorable, so the hydrogen that had been on the oxygen will come off and form this product, an ether.

{continuation of lab description}

Silver nitrate stains clothes and skin. {"temporary tattoo"}

Cleaning a test tube

If you wanted to clean a test tube out, how much liquid do you think you should put in here to clean it out with? If you want to clean a test tube out, what do you think the best amount of liquid to put in here would be to efficiently clean the test tube? There.

For all of you who said stop way before, if you fill your test tube up to here and shake it, the liquid's hardly going to get shook around. You need to physically agitate that liquid if you're going to have any kind of cleaning action, because sometimes just contact between solute and solvent does nothing. If you've already got it all the way filled up, there's no head space, you could say, to be able to shake it. You need just a milliliter of acetone, for example, shake that around, pour it out, that does a much better job. Students seem to love to bathe in acetone, because they think it's no more expensive than water. But it is. The shipping costs are more than the acetone itself. It's a liquid, it's flammable, it can only be shipped in certain ways, so it's pricey.

{acetone policy}

Methyl and primary alkyl halides react more quickly by this mechanism than 2° or 3° alkyl halides because there is less steric hindrance around the reaction site.

Inversion of configuration – geometry @ a stereocenter is inverted during a reaction.

regiochemisry – refers to whether a reaction occurs at only one site or @ multiple sites

Bimolecular nucleophilic substitution (SN2)

$R = k[[]][[]]$

RLS – rate-limiting step – individual step with the largest activation energy

Both the nucleophile and the substrate react simultaneously in the RLS.

conjugation – a bonding interaction that involves more than two atoms.

hyperconjugation – a non-bonding orbital interaction

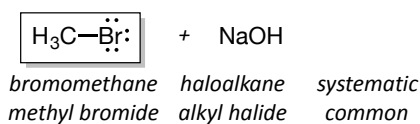
In this type of reaction, 3° alkyl halides are much more reactive than methyl or 1° alkyl halides because the carbocation formed during the reaction is more stable.

Unimolecular Nucleophilic Substitution (SN1)

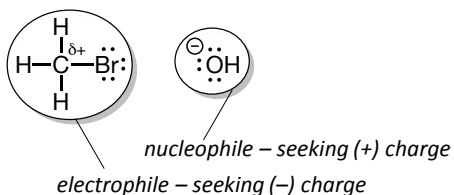
Only one molecule is involved in the RLS (formation of the carbocation)

Structures

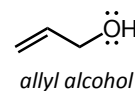
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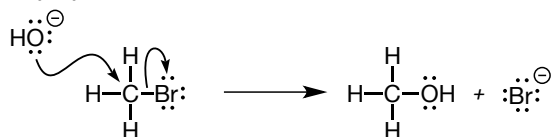
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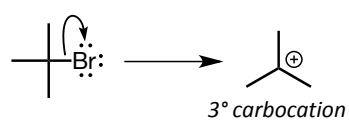
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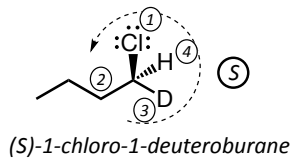
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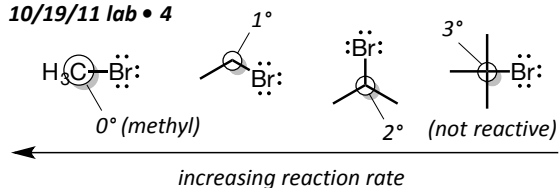
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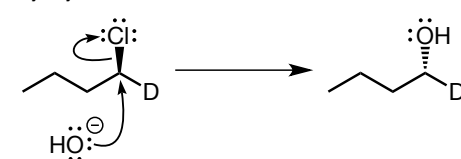
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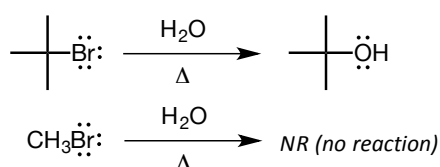
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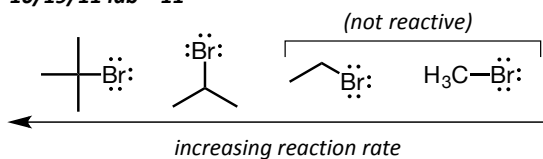
10/19/11 lab • 6



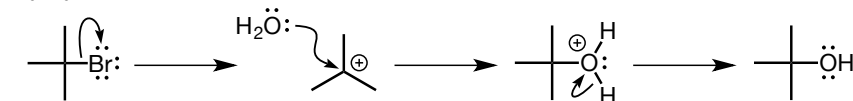
10/19/11 lab • 7



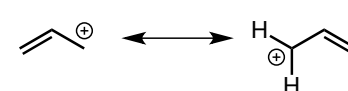
10/19/11 lab • 11



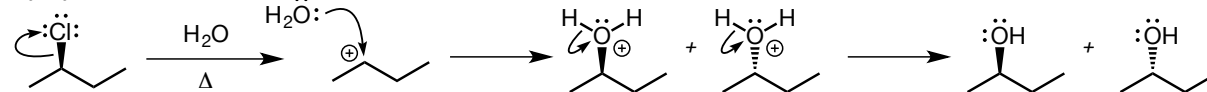
10/19/11 lab • 12



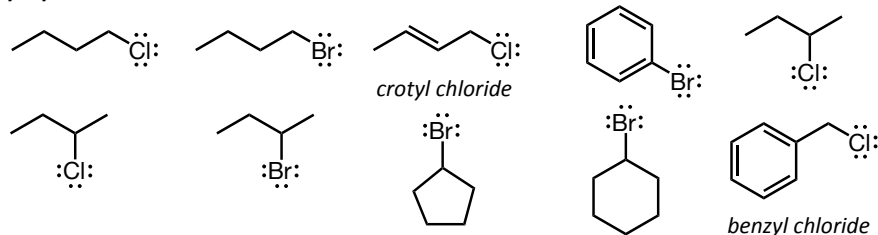
10/19/11 lab • 10



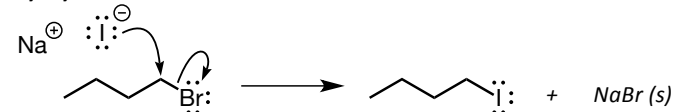
10/19/11 lab • 13



10/19/11 lab • 14



10/19/11 lab • 15



10/19/11 lab • 15

