## Lab 7B • 10/20/11

We have bromomethane and sodium hydroxide.

Nomenclature of alkyl halides

Systematically, this would be called bromomethane. Notice that, much like ethanol, where, because an –OH group, no matter where you put it on ethanol, would be called carbon 1, there's no way to have 2-ethanol, so we just leave the number out. We don't need a number for bromo, in this case, because if it's methane, there's only one place the bromo can go. It's not 1-bromomethane, it's just bromomethane. Related to that, the general name for this functional group, systematically, would be haloalkane. But, as will often still be found on many (particularly older) reagent bottles, chemists still very frequently refer to those compounds with their common names. For common names, you name the alkane portion of it as a substituent, and then tack on the name of the halogen. You can also call this methyl bromide. The function group name, in that case, would be alkyl halide. This is for common names.

Why, do you guess, a reaction between these two molecules might occur? Where do you think, structurally, the reactive bit of bromomethane is? If hydroxide's going to attack, where's it going to attack? Lone pairs? It wouldn't quite make sense for electrons to attack other electrons, since they're both negatively charged. But bromine is an electronegative element; what is that going to mean for the carbon that it's attached to? It's going to have a slight positive to it. There are terms we can use to describe if something is electron-deficient or electron-heavy, or the way we cast it is we say something wishes to have electrons, something wishes to have positive charge. The two terms we could use are electrophile – means electron-liking, which means something that seeks negative charge; its complement would be nucleophile, nucleus-liking, because nuclei are positively charged – that would be a situation in which something seeks positive charge. In this example reaction, the electrophile is the alkyl halide, because you've got this delta positive center that can eventually be attacked, so it's going to get electrons. The nucleophile would be hydroxide; it's got a negative charge, so it's going to be attracted to something that has positive charge.

Let's see what the mechanism of the reaction would look like. Due to the polarity of the molecule, hydroxide is going to be drawn towards that carbon. The base of the arrow shows where the electrons are coming from (the hydroxide), and the head of the arrow shows where the electrons are going to, in this case towards carbon, which means they're going to make a bond with carbon. But carbon is tetravalent; if you make a new bond with carbon, something has to give. Which one of these bonds would make more sense to give, the carbon bromine bond, or the carbon-hydrogen bond? Carbon-bromine bond; it's already polarized, and on top of that, once bromine comes off, that's bromide, which we know tends to want to exist in [aqueous] solution, doesn't mind existing in solution, as long as there's no silver, mercury, or lead around. So bromide will come off and will form methanol as out main product, plus again we have that bromide ion.

It turns out that the structure of the alkyl halide used in this reaction heavily influences the rate of this reaction. Let's look at this series of compounds: methyl bromide, bromoethane, 2-bromopropane (or isopropyl bromide), and then tert-butyl bromide (or 2-bromo-2-methylpropane). In that last compound, what type of carbon do we have where the bromine's attached? What kind of alkyl halide is this? Tertiary, because at that point, there's three other carbons attached. The isopropyl bromide, the 2-bromopropane, what kind of alkyl halide is it? Secondary. Bromomethane, primary. Methyl bromide? It's not even primary; there aren't any other carbons. Sometimes, in numbers, I'll express it as 0°, but usually we'll just say methyl; it's its own special case. If you take methyl bromide, ethyl bromide, isopropyl bromide and tert-butyl bromide and react them all with sodium hydroxide, distinct different in reaction rate. In fact, tertiary alkyl halides are, for the most part, not reactive, at least not in this kind of reaction.

What would be a logical reason why this reactivity difference exists? Why would the methyl halide react so much more quickly than a tertiary alkyl halide? Stability does matter, but it is not the prime reason in this case. Steric hinderance, which is the idea that you can have crowding from electron clouds from atoms that are getting too close to each other. The same reason applies here. That t-butyl bromide: it's really deceptive on paper, because it looks like just a coupe of sticks. But remember, that's three methyl groups that each have three hydrogens, so there's this cloud of electrons that surrounds the reactive center. What if the reaction depends, as this mechanism seems to show, on hydroxide being able to get to that reactive carbon? If you've got all of this garbage in the way, it cant react. Versus a methyl group, that's got nothing around it, practically; it's just got these little hydrogens. It's easy for that nucleophile, the hydroxide, to come in and react. That is the explanation in this case.

Methyl and primary alkyl halides react more quickly by this mechanism than secondary or tertiary alkyl halides since there is much less steric hinderance around the reaction site. This is our first practical instance of how structure affects reactivity. Put too much stuff in the way of that nucleophile getting to that site, and the reaction just won't occur.

Now let's talk about a couple other of the important aspects of this mechanism. I'm going to take a primary alkyl halide, but I'm going to take a chiral one. {commentary of place of stereochemistry in textbooks}

What's the name of that molecule? Is it R or S? Remember that stereodescriptors go at the front of the name. S, because the halogen has priority one, carbon number two, deuterium number three, hydrogen's in the back where it should be for visualization. 1, 2, 3 in a counterclockwise direction: it is S. Which position is the chlorine at? This is the last carbon. That's a deuterium over here, and even though there's a line going that way, that's just to show that the deuterium is present. This is not a carbon at this position. Where the chlorine is is position one. You have a chlorine and a deuterium there, so this would be (S)-1-chloro-1-deuterobutane.

What happens during this reaction with hydroxide? Hydroxide is coming in, and at the same time, chlorine is being kicked out. The way that that carbon chlorine bond breaks is when that hydroxide comes in, it put electrons into the antibonding orbital of the carbon-chlorine bond. If you put electrons into an antibonding orbital, that will cause a bond to break. That's exactly what's going on here. Geometry-wise, the antibonding orbital points the opposite way from the bonding orbital. If that's going to occur, hydroxide has to come from the back of where the chlorine is oriented. That means that, once this reaction's completed, we're going to have a product that looks like this, where now the –OH group is now pointed in the opposite way the chlorine had been. This is known as inversion of configuration, where the geometry at a stereocenter inverts during a reaction. This inversion is a critical feature of the mechanism, because if one form of a molecule could be helpful but its mirror image is harmful, it entirely matters which one that you're making. One of the mechanism aspects you have to learn is that this kind of attack causes inversion of stereochemistry.

Let's talk about another aspect: how this reaction is named. This is known as bimolecular nucleophilic substitution; in general chemistry terminology, this could be called a single-replacement reaction. You put one group on, another leaves at the same time. Nucleophilic substitution, because it's a nucleophile that's driving the reaction. What does the term bimolecular mean? Two molecules in what situation? In a rate law. You've got R, and you've got some set of concentrations, what else goes in there? k, the rate constant. How do you know which reagents go in a rate law? Limiting reagent, that's a stoichiometric issue, not a kinetic issue. The rate-limiting step. This is a reaction coordinate diagram, which shows you the energy of the reaction as it goes from reactants to products. The whole point of this type of diagram is so we can see where we have different kinds of activation energy. For example, if you have a match, you can stare at it all day long, and it's not going to light – at least it better not, or you're super-special. Take that and strike that against a striker, all of a sudden, the match busts into flames; we know that matches like to burn? Why didn't it burn beforehand? It takes some energy to get up to the toughest point of a reaction, what's known as the transition state. Once you get past that, the reaction easily occurs. The equivalent idea would be like an amusement park ride; you get over that first top hill, and, if everything goes right, it's all just downhill from there.

How's this related to the rate-limiting step? As you can see, a reaction might have multiple individual steps. Each top of this diagram I drew is a different transition state, which means a different fundamental reaction step. Notice that the first activation energy is much taller than the second activation energy. Normally, the rate-limiting step is assigned to the step that has the largest activation energy. Because it's the reaction step with the large activation energy, we say that it controls the rate of the reaction. Why do we make that statement? How about the Arrhenius expression, which lets us directly related activation energy to a rate constant. Once you know a specific activation energy, we can then notice that there's always an energy distribution. For example, at room temperature, water evaporates, even though you're not near the normal 100 °C boiling point (or you better not be anywhere near the boiling point). How can water evaporate, then? Because not all of the molecules are moving at the same pace. A certain fraction of molecules have more than that minimum necessary energy, and they evaporate. Exactly the same concept in kinetics: you determine an activation energy, and then if molecules have more than that, they will react. You raise the activation energy, you lower the fraction of molecules that have enough energy, and you lower the rate of the reaction. The rate-limiting step is the step of the reaction that has the largest activation energy.

If you look at the mechanism of this reaction, how many steps are there? Not how many arrows, how many steps? Do I have any information associated with these arrows that says one happens first and then the next and then the next? No. That's because when you write everything in one diagram like this, it means it's simultaneous or, the term we use for mechanisms, concerted. There is only one reaction step. How many molecules are involved in that step? Two. That's why it's bimolecular, because in the only step, which is therefore the rate-limiting step, two molecules are involved, so if you change the concentration of either of them, the reaction rate changes. That is why this mechanism is called bimolecular nucleophilic substitution. Both the nucleophile and what I refer to as the substrate – meaning the primary organic molecule that's being operated on by the set of reagents – react simultaneously in the only reaction step; that's why it's called bimolecular.

Let's see this alternate reaction pathway. This time, I'll take a tertiary alkyl halide, but instead of hydroxide, I'll use water. What does the triangle pointing up mean? Heat. So, this is a tertiary alkyl halide that'll be put in water and heated up. Turns out, you'll make an alcohol. But just a moment ago we saw a reaction with hydroxide where exactly this would not happen. It's backwards somehow. In fact, to continue that trend, if we take methyl bromide and react it not with hydroxide but with water and heat, no reaction occurs, exactly backwards of the behavior we saw with that hydroxide. What do you think might be going on in this case? Hydroxide is negatively charged, so it can more actively attack and interact with that partially-positively charged carbon. But here we have neutral water. Would you saw water is as good a nucleophile as hydroxide is? What does nucleophile mean? Wanting to have positive charge. Do you think water as badly wants positve charge as hydroxide does? Why not? It's neutral. Hydroxide had a negative on it, which of course means it want's to have positive.

Water, at best, we could say that the oxygen has a partial negative charge, so yeah, it might its way to that partially positively-charged carbon, but it's not going to make the type of attack that hydroxide did.

So what if, instead, this reaction happens because bromide just comes off. Instead of having a partial positive charge, we have a full positive charge. That might be much more attractive to something that's neutral but polar like water. If this is the case, then what we really have to ask is why can this carbocation formation happen with a tertiary alkyl halide, but it appears it won't happen at all with a methyl halide? Why is there a difference in rate? It is the kind of carbon it's on, tertiary versus non-tertiary. What if we have electrons on other parts of the molecule that somehow kinda bleed over and somehow stabilize that positive charge? That's called hyperconjugation. But before telling you about what hyperconjugation is, I should tell you what conjugation is.

There's a common name for having something substituted at the carbon next to a double bond. For example, this compound has the common name allyl alcohol. Similarly, this carbocation I wrote up is called the allyl cation. Very common ion. Which of those two structures that I wrote for the cation is correct? Can two structures be correct at the same time? They're the same structure and they're not; one shows a double bond on the left and the other is on the right? Neither structure is correct; how can two things simultaneously be correct? They're not. That means that both of them, individually, are wrong. What's going on? Maybe if we made a SMOG it would be much clearer.

What is the hybridization of the leftmost carbon? sp2. Why? There's two hydrogens and a carbon attached; the double bond doesn't count. We only have three sigma bonds that we're worried about, which means we need three hybrids, which means we used three atomic orbitals so it's s, s, p, that means sp2. What about the middle carbon? It's also sp2; in this case it's two carbons, one hydrogen, but still three sigma bonds. What about the rightmost carbon? sp2. Why? Positive charge means there's a bond missing, there two hydrogens there then a carbon. All three of these are sp2, so let's draw the SMOG for it. Since each carbon is sp2 hybridized, each carbon has a p orbital. Here's the question: which pair of p orbitals do I connect? If the two on the left are close enough to overlap, aren't the two on the right close enough to overlap as well? The answer is yes. In real life, the length of the bond between the two carbons is in between that of a single and a double bond. You don't have a pi bond; you have a pi system. That is resonance. Resonance is not that a molecule exists in two different forms. It exists in one form that we fail to be able to write down on paper. The closest we can do is to write something like this, to show a two-electron, three-center bond. But we don't do that, or I heavily recommend against it because you can't count electrons. That is the usefulness of using proper line structures, because at least you can count and say this many electrons are here and here and here. We have dotted lines; what's a dotted line mean?

This is why we have multiple resonance structures, because you can't write one, because it doesn't show you truly what the structure of the molecule is. You could say that both of these structure are correct, but the better way of saying it is if you combined the two structures and blended them, that's what's correct. Either one individually fails to show this extended overlap, which is called conjugation. Conjugation is a bonding orbital interaction that involves more than two atoms. So when we had just two atoms involved, we saw how we could make sigma bonds and pi bonds, so we talked about the sigma bonding orbital and the sigma antibonding orbital, the pi bonding orbital, the pi antibonding orbital. When we have three involved, we're going to have a bonding orbital, an antibonding orbital, and in between, we'll have a non-bonding orbital, which is the same energy as if nothing ever happened in the first place. So there are three molecular orbitals in a three-atom conjugated system. There's four in a four-atom system, five in a five-atom system.

Let's take that tertiary carbocation and draw a SMOG for it? What's the hybridization of the central carbon? sp2. Three bonds, sp2. What's the hybridization of any of the methyl groups? It is sp3, because we have three hydrogens plus the carbon that are attached to each one of those positions. {conjugation with s orbitals? hydride shift} As these single bonds rotate, there's interactions that can occur between the sigma bonds on a neighboring carbon with that p orbital. Ignore the fact that I drew some of the interactions with the top versus the bottom. Recognize that, at room temperature at least, the sigma bonds would be constantly rotating, so sometimes the overlap would occur at the top and sometimes it would occur at the bottom. It's not necessarily that all three sides are going to interact simultaneously, it's just that each time that [bond] is turning and bond ends up roughly parallel to the p orbital, some electron density from that sigma bond can pour over to the positive charge, which spreads out the positive charge, which spreads out the burden of handling that positive charge, and therefore makes the molecule more stabilized.

Why does this not happen for the methyl case? If you look at this, we'll see a 90° angle between the sigma bonds in that molecule and the p orbital. Since it's 90°, no overlap occurs; no stabilization occurs. In the tertiary case, there's three neighbors that at different times, one of those neighbors is able to overlap. What we'll find is that in a secondary carbon, there'll be two neighbors. In a primary carbon, there'll only be one neighbor that has this potential to overlap. This explains the order of reactivity of alkyl halides.

Hyperconjugation is non-bonding orbital interactions involving more than two atoms. In this case, it involves a sigma bond between carbon and hydrogen, and another carbon – so three atoms involved. Non-bonding, because just a little bit of the electron density is moving around. In fact, it's coming from something that was already bonding.

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Hyperconjugation – we have it in the tertiary case, we don't have it in the methyl case. So if we look at t-butyl bromide, versus isopropyl bromide, bromoethane, or bromomethane, that in this reaction mechanism, the reaction rates are backwards from what we saw previously. Why is that? Tertiary and secondary alkyl halides are much more reactive in this mechanism than primary or methyl alkyl halides because the carbocation formed during the reaction is more stable.

So now let's look at the full mechanism for the reaction. It starts by making the carbocation. Once we have the carbocation, then something like water can form a new bond. But since water started out neutral, there is one more reaction step that occurs, where one or the other of the hydrogens comes off, in an acid-base style reaction. That will then leave us with the neutral alcohol. In this case, water does not have that power to come in and substitute; it has to wait for the halogen to fall off; that depends on the carbocation stability. So tertiaries react more quickly because the carbocation forms more quickly. That ties us into the name for this reaction: unimolecular nucleophilic substitution (Sn1).

Why is it called unimolecular? How many steps are in this reaction? More than one; how many? Three. How do I know that? Here's one reaction step, and you see what the next intermediate is. When you're writing a mechanism, that's what this reaction forward arrow means, you're done with that step. Then there's a bond forming even; next step. Then a bond breaking event. So three different processes occur. Out of those three, which one do you think is the energetically least-favorable? One of those choices you'd hopefully be able to eliminate right away: does forming a bond or breaking a bond release energy? Forming a bond; that's why bonds form, because energy's released. Remember that in the classical description, we saw energy drop because we had the right kind of positive and negative charge interacting. In the quantum description, it's because in the bonding orbital, charge is between two nuclei, which still means a better electrostatic interaction. That's why energy is released. So first step and last step where you are breaking a bond, you have to add energy in. But which of those two steps do you think is worse? Oxygen doesn't like to be positively-charged, does it? It's electronegative. So, getting rid of that hydrogen, it's actually a very quick and easy reaction. It may be a bond breaking event, but it's a really fast bond breaking event. That first one, that's the whole point: making the carbocation is tougher. That first step of the reaction is the rate-limiting step. How many molecules are involved in the rate-limiting step? Only one; that's why it's called unimolecular. Only one molecule, the substrate, is involved in the rate-limiting step: the formation of the carbocation.

The last thing we need to discuss is stereochemistry. Let's say we have a chiral secondary alkyl halide like (R)-2-chlorobutane. When it reacts with water and heat, as we see by this mechanism, it's going to form a carbocation. What is the geometry at that carbocation? That's right, three things attached, trigonal planar, trigonal – planar. Meaning, for the most part, that there's no difference from if you look at the molecule from the top or the bottom at that position, because it's in a plane. So if water were to come in and attack, baring any other complications due to things happening in solution that we haven't discussed yet, ignoring that, if you had a planar molecule, is there any reason why water would prefer to attack from the top or the bottom? No. In fact, you can do both – not on a molecule-by-molecule basis, but since you've got a whole solution of the stuff, any other factors being ignored, half the time it'll attack from the top, half the time it's attack from the bottom. What does that mean? It means we end up with two products, or we will, once the reaction is completed. When water first connects, it's got a positive charge on it, so hydrogen has to come off, and we make a pair of alcohols.

The most common mistake I see in mechanisms is what happens to a hydrogen exactly in this case. The hydrogen comes off, but not the electron. Remember that in reaction mechanisms, the arrows always show where electrons go, not where atoms go. So the electrons from that bond go back to oxygen and just H+ comes off. So you don't write an arrow pointing to the hydrogen because that would be hydride, H–.

This case, when enantiomers are formed in equal proportions, the reaction mixture is racemic, coming from racemus, meaning a bunch of grapes, from which tartaric acid can be isolated, and tartaric acid has multiple forms. If you have this 50/50 mixture of enantiomers of tartaric acid as was isolated at one point, that mixture will be optically inactive. Why? It's kind of similar logic to the meso molecule case. In a meso molecule, half the molecule cancels out the other half. In a racemic mixture, you have a full molecule that's a mirror image with another molecule, that's what enantiomers mean. If you have exactly the same amount of each enantiomer, statistically in solution, that means the optical activity of one half of the solution cancels out the other half. The molecules are chiral; it's not what we had with the meso, they are chiral, but you've got two of them, and that's why the solution is not optically active. So racemic mixtures are not optically active because half of the molecules cancel the optical rotation of the other half.

{description of lab procedure}

crotyl; benzyl

For Sn2, it's a mixture of sodium iodide in acetone. Acetone is an organic molecule, but it's a very polar one – polar enough that it's soluble in water. Polar enough that sodium iodide has non-zero solubility in acetone – but not great solubility. Sodium iodide is more soluble that sodium bromide or sodium chloride. There's a solubility trick that's going to be played in this reaction. To show you an example mechanism, what happens is iodide, although it can leave a molecule, it can also be a nucleophile, so it could attack and displace the bromide.

In theory, the bromide could turn right back around and attack, but because sodium bromide is less soluble in acetone than sodium iodide, it precipitates before it has that chance. If it precipitates out, it's no longer part of the reaction mixture, that means the reaction's being forced forward, if it occurs. So, it's an Sn2 reaction where the halogen's being trapped after it occurs.

What's the set of reagents for Sn1? Somewhat different. It's silver nitrate in ethanol. Probably some residual water in there as well; probably enhances the solubility of silver nitrate. [warning about silver nitrate]. What's the mechanism that occurs? It's Sn1. The first step is that a halogen comes off. There's silver around in solution, so it's another kind of trick being played, where if the halide comes off, it'll just fall out of solution. The ethanol, which is the solvent, happens also to be a reagent; that's very typical for Sn1 reactions. Ethanol floods the reaction; it's able to substitute at that carbocation, much like water would. Similar to water, the oxygen will, after reacting, be temporarily positively charged, until it relieves that positive charge by losing a hydrogen. You'll end up forming ethers as your products. How do you know a reaction's occurred? You'll see a color charge, you'll see it go cloudy, or, most importantly, you'll see a precipitate. [warning about false positives]

[remainder of lab procedure]
[waste disposal]

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Methyl and primary alkyl halides react much more quickly by this mechanism than 2° or 3° alkyl halides since there is much less steric hinderance around the reaction site.
Inversion of configuration – the geometry of a stereocenter inverts during a reaction.

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 only reaction step.

conjugation – a bonding orbital interaction that involves more than two atoms.
hyperconjugation – a non-bonding orbital interaction involving more than two atoms.

3° and 2° alkyl halides are much more reactive in this mechanism that 1° or methyl halides because the carbocation formed during the reaction is much more stable.

Unimolecular Nucleophilic Substitution (SN1)
Only one molecule – the substrate – is involved in the RLS (formation of the carbocation)

When enantiomers are formed in equal proportions, the reaction mixture is racemic. Racemic mixtures are not optically active because half of the molecules cancel the optical rotation of the other half.

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Structures

Identical to those from lab 7A (10/19/12)