Hey guys! Hopefully this week goes well for you all, and good luck on your tests! This week continues our focus on compounds with carbonyls, as we dive into more complex reactions. **In-person group tutoring sessions will take place every Wednesday from 5:15 to 6:15 PM in Sid Rich Room 74.** For more information about tutoring, and getting help, you can follow the link: [www.baylor.edu/tutoring](http://www.baylor.edu/tutoring).

**TOPIC OF THE WEEK: Alpha Carbon Chemistry (Chapter 21)**

**Keywords:** Enol, Enolates, Aldol, Condensation, Alpha Carbon

**Enols, Enolates and Aldols:**
As you are all likely familiar with by now, there is a lot you can do with ketone groups on a molecule. However, by having a ketone tautomerize (like a form of resonance) to an enol, we can unlock even more reactions. For reference, all an enol is is an isomer of a ketone, by moving the double bond, and getting a hydroxyl group instead, using resonance.

![Ketone Tautomer](image1)

![Enol Tautomer](image2)

Usually, equilibrium will favor the ketone form, and with the enol being in small yields. Despite this, there is a way in which we can have an equal amount of the two tautomers, in the form of an enolate, which is achieved by plucking a proton off of either the ketone or enol.

![Enolate](image3)

One of the useful qualities of having an enol tautomer of ketones is that it allows us to perform addition of halogens to the enols double bond (**at an alpha carbon**), while reverting back to the ketone form. For example, this is a possible halogenation reaction (notice how the more substituted carbon is favored):

![Halogenation Reaction](image4)
If we look at the mechanism, we can see that the bromine is being added to the enol, which then reverts back to having a ketone functional group.

As mentioned above, in this reaction, the bromine will always be added to the more substituted carbon. Unfortunately, there is little we can do to add halogens to a less substituted carbon. In doing so, we likely will add more than one halogen, and it is difficult to isolate a desired product. However, while this may not be so great for halogens, it is quite good at replacing an alpha carbon with a hydroxyl group.

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**HIGHLIGHT #1: Aldol Addition and Condensation**

**Aldol Addition:**
The most prevalent and important reactions you all will be covering this chapter are the combination of aldehydes to create different structures. The simplest one to start with is aldol condensation, which usually involves two aldehydes or symmetrical ketones that will add together to yield an aldol, or a molecule with a carbonyl and adjacent hydroxyl group.
By using a base to pull off a hydrogen from the alpha carbon, we can impart a negative charge on the alpha carbon. Since carbonyls have a net dipole (with the carbon having the partial positive charge) the negatively charged alpha carbon will attack the carbonyl carbon, forming a bond between the two aldehydes, giving us an aldol.

These aldols can also be condensed. This simply means that we use a strong base to eliminate the hydroxyl end of the aldol, leaving a double bond. Since double bonds are an Ochem 1 concept, you should be familiar with them favoring a more substituted position, as well as the major product usually being the trans isomer.

**Crossed Aldol Addition:**

For the above reaction, we only used two of the same aldehydes. However, we can use two different aldehydes, in a reaction that is a crossed aldol addition. Because we are using two different starting molecules however, there is the possibility for multiple different products to form.
Of course, using certain molecules like formaldehyde (which has no alpha carbon to pull hydrogens from) can help to cut down on the amount of products we may create.

**Limiting the number of alpha carbons cuts down on products**

![Two unique alpha carbons](image)

From the two aldehydes, it can be hard to isolate a single product.

**Claisen Condensations:**

Similarly to aldehydes and ketones, esters can also add with each other to create new molecules. This reaction follows the same ideas and patterns as the ones before it, using a base to pull off an available hydrogen, which then allows one ester to attack the other at a carbonyl. We can have both normal, and crossed reactions, with a multitude of results. It is important to note that instead of yielding an aldol, one of the OR groups will instead act as a leaving group, allowing for two ketones on the molecule. Furthermore, you will see that on the central carbon, a negative charge and lone pair is left. This is done using a strong base, and will give extra stability to the molecule.
Intramolecular Reactions:

Molecules that have two ketones or a ketone and aldehyde have the ability to perform aldol reactions with themselves. Just like all the other reactions mentioned previously, a strong base is used to pull a hydrogen from an alpha carbon. The molecule will then use this carbanion (negatively charged carbon atom) to attack itself, creating a ring structure. In the process of doing so, the hydroxyl of the aldol will be condensed, since the conditions for this reaction require both a base and heat.

PRACTICE PROBLEMS!

1. Provide a synthesis for the following reaction:
2. In this crossed aldol addition, predict the multiple products that may be formed, from the follow two molecules:

3. Provide a mechanism for the following reaction

**THINGS YOU MAY STRUGGLE WITH:**

- A lot of the reactions in this chapter are very convoluted as we are basically just adding together very large molecules. When doing practice problems, and especially during the test, make sure to draw everything out to keep track of the molecules.
- Going off that idea, sometimes you may forget that an alpha carbon has no hydrogens to give off. Because of this it is important sometimes to draw out the hydrogens on some of the carbons to make sure the reaction will proceed correctly.

**Answers:**

1. For this first problem, the only difference we have between the two molecules is the terminal hydroxyl that is added in the product. Because of this we know that we either need to add the hydroxyl directly to the chain, or to a double bond. While we do not know of any ways to add the OH$^{-}$ group directly, we know that if we were to eliminate something, the hydroxyl could be added anti-Mark to the double bond. One of the things we do know how to add directly is a halogen (in this case bromine), an alpha carbon. We can then easily pull it off, and then add the OH$^{-}$ group to the terminal end.
2. In this problem, we are given a non-symmetrical ketone, and an aldehyde. Because of this, we have three different places where we could pull a proton off an alpha carbon:

For the ketone enolate, we can of course get two products; one where the methyl end attacks the aldehyde or where the ethyl end attacks:

Additionally, our aldehyde can attack the ketone, at the carbonyl to give a single product:
First off, we need a base to pull off a proton to start the reaction:

Next, the carbanion will attack the other ketone. I moved around the molecule a bit, to make it look more like its cyclic product. Then, the former ketone, now almost a hydroxyl, will pluck off a hydrogen from water to get to be a hydroxyl.

Now, another dosage of base will come to pull off another hydrogen, to create a double bond in the most substituted place, to allow our hydroxyl to leave.
All tables are courtesy of Organic Chemistry by David Klein. All drawings of molecules and mechanisms are made by me.