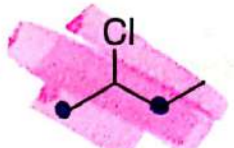
8.6 THE REGIOCHEMISTRY IS CONTAINED WITHIN THE MECHANISM

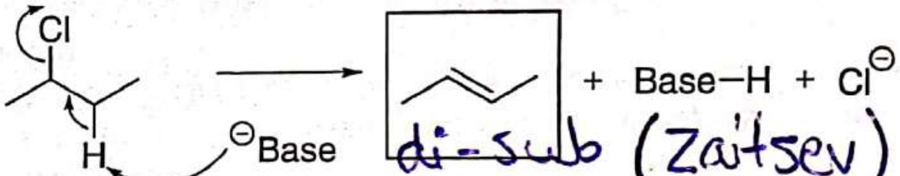
Regiochemistry refers to *where* the reaction takes place. In other words, in what region of the molecule is the reaction taking place? Let's see examples of this for different types of reactions. In the process, we will uncover some new terminology as we learn about different reactions.

Let's consider elimination reactions. When we eliminate H and X (where X is some leaving group that can leave with a negative charge, like Cl or Br), it is possible to form the double bond in different locations. Consider the following compound:



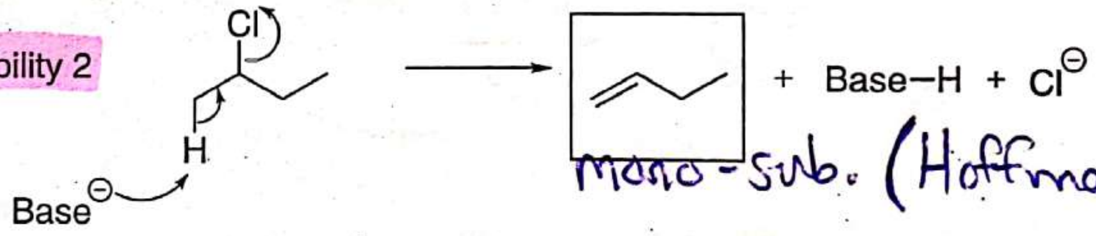
This compound can undergo two possible elimination reactions (to make it easier to see, we are drawing the H that gets eliminated in each case, even though we usually do not draw hydrogen atoms on bond-line drawings):

Possibility 1



di-sub (Zaitsev)

Possibility 2



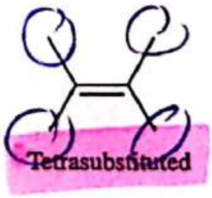
mono-sub. (Hoffman)

Where does the double bond form? This is a question of regiochemistry. We distinguish between these two possibilities by considering how many groups are attached to each double bond. Double bonds can have anywhere from 1 to 4 groups attached to them:

Monosubstituted

Disubstituted

Trisubstituted

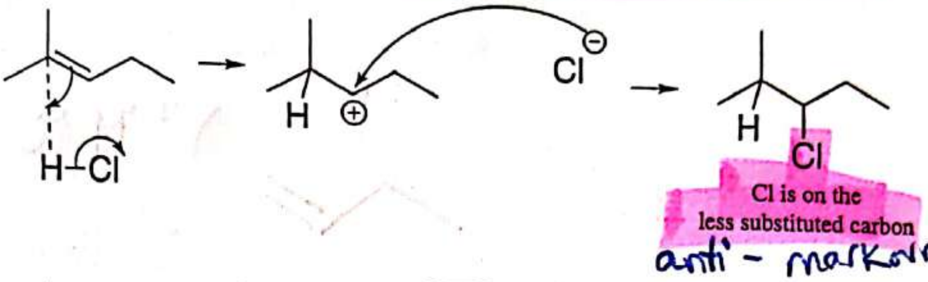


Tetrasubstituted

So if we look back at the reaction above, we find that the two possible products are monosubstituted and disubstituted double bonds. Whenever we have an elimination reaction where more than one possible double bond can be formed, we have names for the different products based on which one is more substituted and which one is less substituted. The more substituted product is called the Zaitsev product, and the less substituted product is called the Hoffmann product. Usually, we get the Zaitsev product, but under special circumstances we get the Hoffman product. You will learn about this in detail in your textbook when you cover elimination reactions. For now, you just need to realize that this is an issue of regiochemistry. The difference between the Zaitsev product and the Hoffman has to do with where the double bond formed. This is regiochemistry.

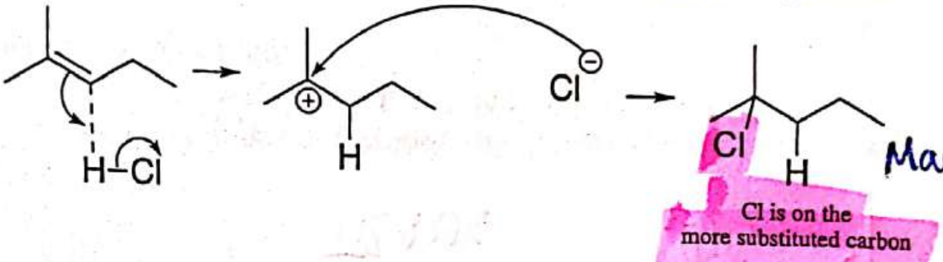
Let's consider another example of regiochemistry, in a completely different type of reaction. Consider the addition reaction of HCl across a double bond:

Possibility 1



anti - markovnikov

Possibility 2



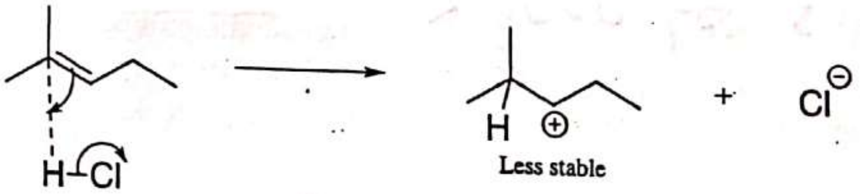
Markovnikov

There are two possible ways to add the H and the Cl. Which product do we get?

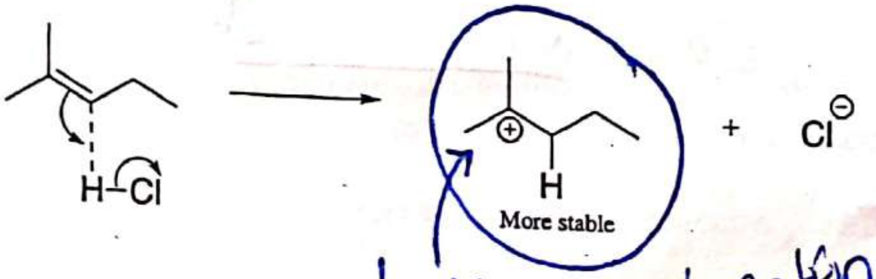
One possibility would be to put the Cl on the less substituted carbon (carbon connected to two other carbon atoms), and the other possibility would be to put the Cl on the more substituted carbon (carbon connected to three other carbon atoms). If we put the Cl on the more substituted carbon, we call this a Markovnikov addition. If we put the Cl on the less substituted carbon, we call it an anti-Markovnikov addition. How do we know whether we get Markovnikov addition or anti-Markovnikov addition? This is an issue of regiochemistry.

For the reaction above, let's analyze the two possible outcomes. In each case, the first step involves the electrons of the double bond attacking the proton of HCl to form a carbocation (a carbon with a positive charge). The difference between the two possibilities is where the carbocation is formed:

Possibility 1

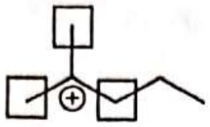


Possibility 2

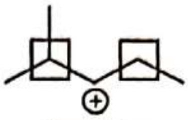


tertiary carbocation
3°

Recall that alkyl groups are electron donating, so the carbocation on the bottom (called a tertiary carbocation because it has three alkyl groups) will be more stable than the carbocation on the top (called a secondary carbocation because it has only two alkyl groups).

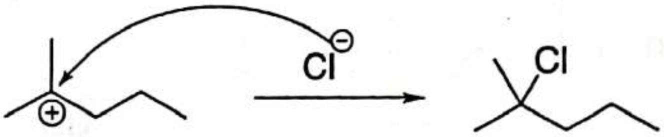


Tertiary
(more stable)



Secondary
(less stable)

Therefore, possibility 2 is a better mechanism (because it involves a more stable intermediate. If we follow the last step of the mechanism for possibility 2, we see that the Cl will attach where the carbocation is, which will be at the more substituted carbon:



We see that the final position of the chlorine is determined by the stability of the intermediate carbocation, which becomes evident as we work through the mechanism. Since the chlorine ends up at the more substituted carbon, we call this a Markovnikov addition. The mechanism for this reaction helped explain the regiochemistry of the reaction.

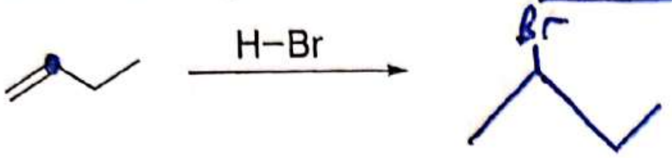
Sometimes regiochemistry is not an issue. For example, if we are adding H and H across a double bond, then it does not matter which carbon gets the first H and which carbon gets the second H. Either way, they both end up with an H. Similarly, if we add two OH groups across a double bond, regiochemistry also does not matter. Any time we add two of the same group across a double bond, we do not have to worry about the regiochemistry.

Here is where we get back to mechanisms. Whether we are talking about Zaitsev vs. Hoffman elimination reactions or about Markovnikov vs. anti-Markovnikov addition reactions, the explanation of the regiochemistry for every reaction is contained within the mechanism. If we completely understand the mechanism, then we will understand why the regiochemistry had to be the way it turned out. By understanding the mechanism, we eliminate the need to memorize the regiochemistry for every reaction. With every reaction you encounter, you should consider the regiochemistry of the reaction and look at the mechanism for an explanation of the regiochemistry.

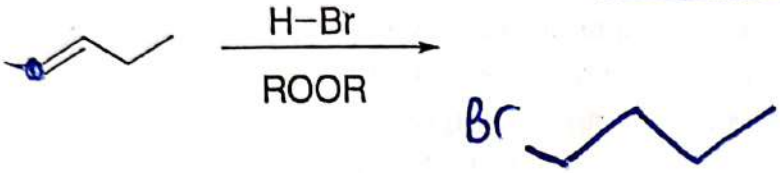
PROBLEMS You will, over the course of your studies, learn the mechanisms for the following reactions. In the meantime, you will be given the regiochemical information that you need to answer each of the problems below. These problems are intended to ensure that you understand what regiochemistry means.

8.34 Consider the reaction shown. If you were to add HBr across the double bond, what would the product be? Assume a Markovnikov addition.

↳ "more"



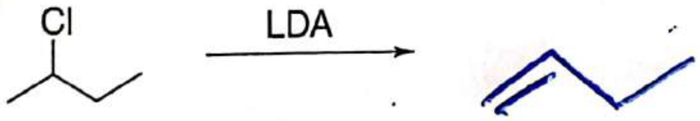
8.35 When you do the same reaction (as above) in the presence of peroxides (R-O-O-R), you get an anti-Markovnikov addition of HBr across the double bond. Draw the product of an anti-Markovnikov addition. → Br on Less sub. C



8.36 Consider the elimination reaction below, which uses a strong base. The product will be a double bond. This reaction will produce two Zaitsev products. One will be cis and one will be trans. Draw these products, and identify which is cis and which is trans.

↳ more sub. 2x bond

8.37 Consider the elimination reaction below, which uses a strong, sterically hindered base (LDA). The product will be a double bond. This reaction will produce the Hoffmann product. Draw this product.

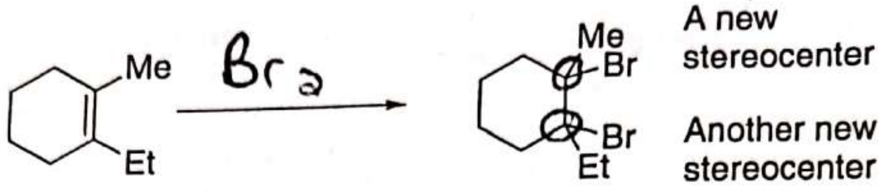


↳ less sub. 2x bond

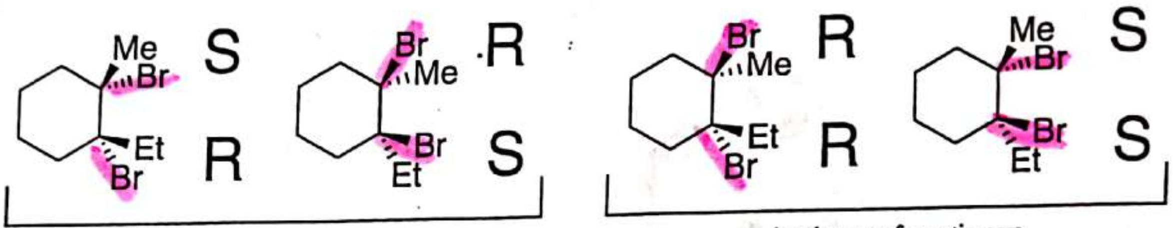
8.7 THE STEREOCHEMISTRY IS CONTAINED WITHIN THE MECHANISM

Stereochemistry is all about configurations of stereocenters (R vs. S) and double bonds (E vs. Z). Whenever we have a reaction where we are forming a stereocenter, we need to ask whether we get a racemic mixture (equal amounts of R and S) or only one configuration. And, if so, why? Also, whenever we form a double bond, we need to ask whether we get both E and Z isomers or only one of them? And, if so, why?

This information is also contained within the mechanism. Let's see an example. Consider the addition of Br and Br across a double bond. We already saw that we don't need to worry about the regiochemistry of this reaction, because we are adding two of the same group. But what about the stereochemistry? We are creating two new stereocenters:



Each stereocenter has two possibilities (R or S). Since there are two stereocenters, we will have four total possibilitites: SR, RS, RR, and SS. These four compounds represent two sets of enantiomers:

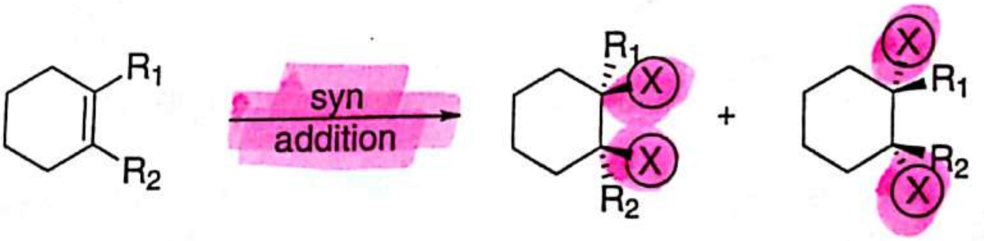


One set of enantiomers,
Br and Br are on the same side of the ring

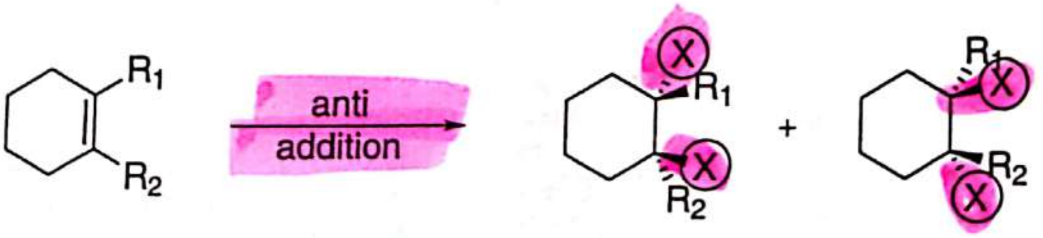
Another set of enantiomers,
Br and Br are on opposite sides of the ring

How many of them do we get? Do we get both sets of enantiomers as our products (meaning all four products), or do we only get one set (meaning two out of the four possible products)? This depends on how the reaction took place.

If an addition reaction can take place only through a mechanism that allows a syn addition, then the two groups that we added must be on the same side of the double bond in the product. So we will get only that one set of enantiomers:



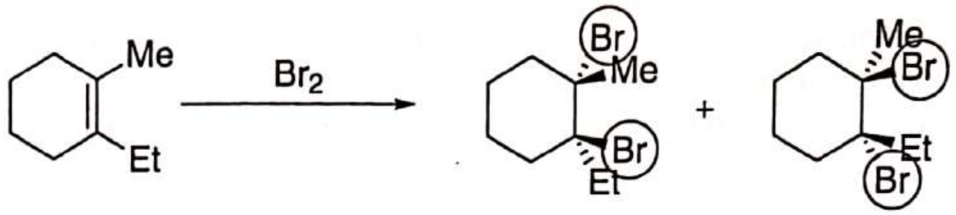
If a reaction can go through only an anti addition, then the two groups we added must be on opposite sides of the double bond. So we will get only the set of enantiomers where the groups are on opposite sides:



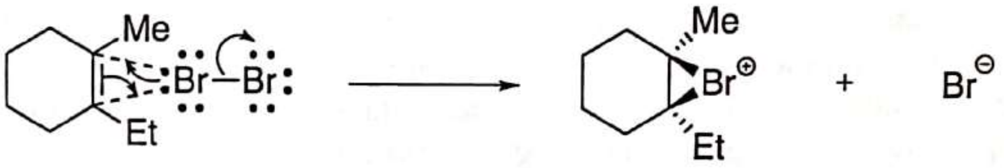
Sometimes, the reaction is not stereoselective. In other words, we get both syn and anti addition. So we get all four products (both sets of enantiomers).

Each reaction will be different. Some will give only syn addition, some will give only anti addition, and others will not be stereoselective. For every addition reaction, we need to know the stereochemistry of the addition, and that information is contained within the mechanism.

So let's go back to our example above with the addition of Br and Br across a double bond. This reaction is an anti addition, so we get only the set of enantiomers that has the two Br groups on opposite sides of the ring:

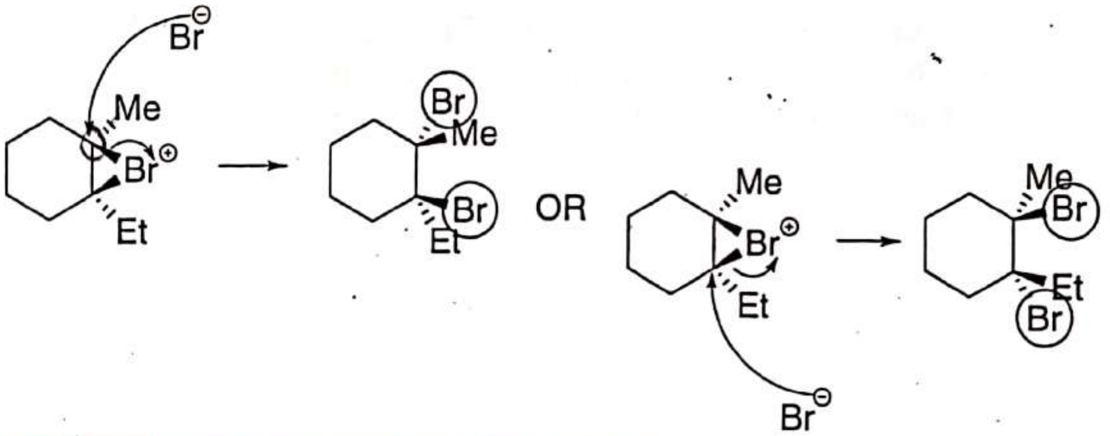


Let's look at the mechanism to understand why. In the first step, we form a bridged intermediate, called a bromonium ion:



In this step, the double bond is acting as a nucleophile that attacks Br_2 (the electrophile in this reaction). The arrows are not going in opposite directions—they are actually moving in a small circle to form a ring.

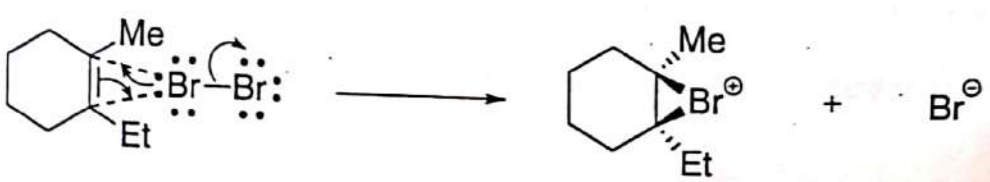
Then, in the next step, the bromide (formed in the first step) comes back and attacks the bromonium ion, opening up the bridge. The bromide can attack either carbon (both possibilities shown below):



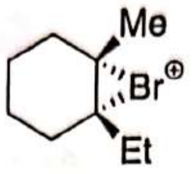
When the bromide attacks, it must attack on the other side of the ring (not the side of the bromonium bridge, but rather on the opposite side of the ring) to break open the bridge. So the addition must be an *anti addition.*

We see that the mechanism explains why the addition must be anti. For every reaction, the stereochemistry will always be explained by the mechanism.

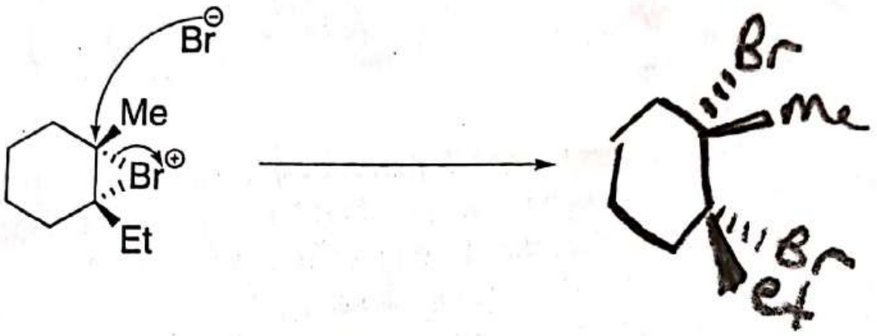
PROBLEM 8.38 In the reaction above, we saw that the first step involved formation of a bromonium ion.

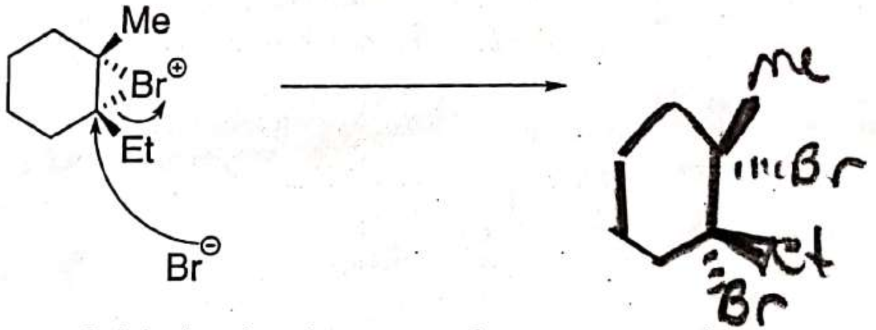


You will notice that the bromonium ion drawn above has the bridge coming out towards you (on wedges), but we did not say at the time that it could also have formed with the bridge going away from you (on dashes):



We did not talk about this at the time, because the end products would still have been the same as the way we did it before. Draw what happens if the bromide (Br⁻) attacks this other bromonium ion. Remember that there are two carbon atoms that the bromide could attack, so draw both possibilities:



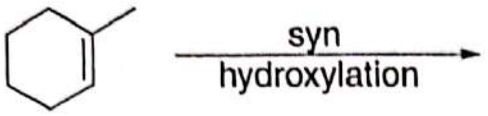


When you finish drawing the two products, compare them to the two products that we got before. You should find that the two products you get here are the same as the two products we got before. Think about why. Remember that the reaction can happen only as an anti addition.

Every new class of reactions (additions, eliminations, substitutions, etc.) has its own terminology for stereochemistry. As you learn each of these classes of reactions, keep a watchful eye on what terminology is used to describe the stereochemistry. Then, look at the mechanism of each reaction within each class, and try to understand why the mechanism dictates the stereochemistry.

PROBLEMS For the following reactions, you will (over the course of your studies) learn the mechanisms for these reactions. In the meantime, you will be given the stereochemical information that you need to answer each of the problems below. These problems are intended to ensure that you understand what stereochemistry means.

8.39 If you add OH and OH across the following double bond in a syn addition, what will the products be?

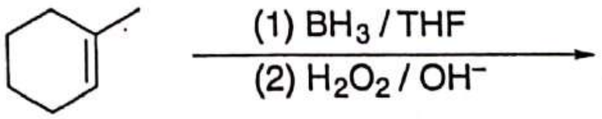


8.40 If you add Br and Br across the following double bond in an anti addition, what will the products be?

8.41 If you add Br and Br across the following double bond in an anti addition, you get only one product. If you draw the two products that you would expect, you will find that they are the same compound (a meso compound). Draw this product.

Do not confuse the concepts of regiochemistry and stereochemistry. For instance, in addition reactions, the term "anti-Markovnikov addition" refers to the *regiochemistry* of the addition, but the term "anti" refers to the *stereochemistry* of the addition. Students often confuse these concepts (probably because both terms have the word "anti"). It is possible for an addition reaction to be anti-Markovnikov and a syn addition (hydroboration is an example that you will learn about at some point in time). You must realize that regiochemistry and stereochemistry are two totally different concepts.

8.42 In the following reaction, we will add H and OH across a double bond. The regiochemistry is anti-Markovnikov, and the stereochemistry is a syn addition. Draw the products you would expect now that you know all of the information.



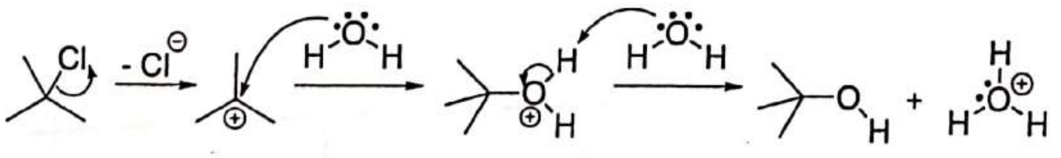
You must know the stereochemistry and regiochemistry for every reaction, and each of them is contained within the mechanism. In the problems above, you were told what to expect for the stereochemistry and the regiochemistry. When you are doing problems in your textbook and on your exams, you will be expected to know what these pieces of information are simply from looking at the reagents. A solid understanding of every mechanism will be an invaluable asset to you in this course.

8.8 A LIST OF MECHANISMS

Now you need to begin to keep a list of all reaction mechanisms that you cover. The rest of the pages in this chapter are set up specifically for you to generate this list in such a way that you will record the critical information: the regiochemistry and the stereochemistry. You should fill in these pages as you proceed through the course and you learn more mechanisms. As your list gets larger, you will have one central place where you can go to review all of the mechanisms.

A few example mechanisms have been filled in for you, so that you can see how to fill in the each mechanism from now on. Depending on the order that your course follows, these reactions may or may not be the first ones you cover. Whatever the case might be, you will definitely see these reactions early on in the course:

<table>
<tr><td>Reaction type
Substitution (S_N2)</td><td>Stereochemistry
Inversion</td><td>Regiochemistry
Not applicable (nucleophile attacks carbon next to LG)</td></tr>
<tr><td colspan="3">
</td></tr>
</table>

<table>
<tr><td>Reaction type
Substitution (S_N1)</td><td>Stereochemistry
Racemization</td><td>Regiochemistry
Not applicable (nucleophile attacks carbon next to LG)</td></tr>
<tr><td colspan="3">
</td></tr>
</table>

Now, for every reaction that you cover, fill in the templates below, and then use this list as a study guide for all of your mechanisms: