

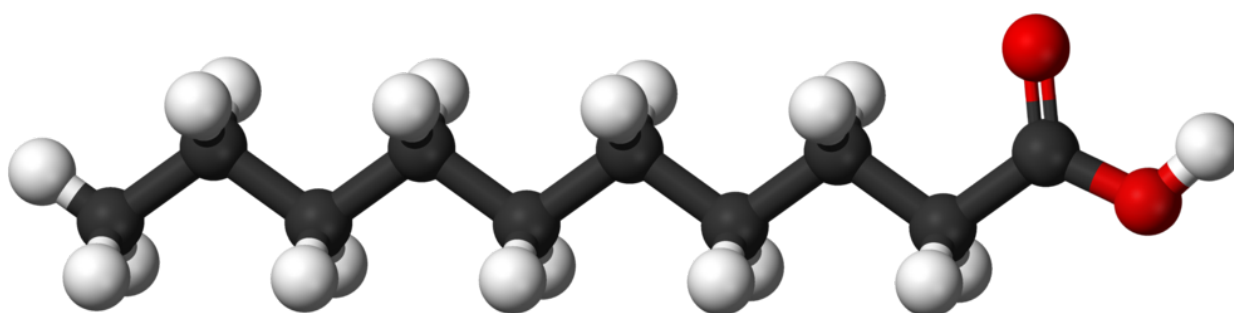
Exam 3 Organic Chemistry Review

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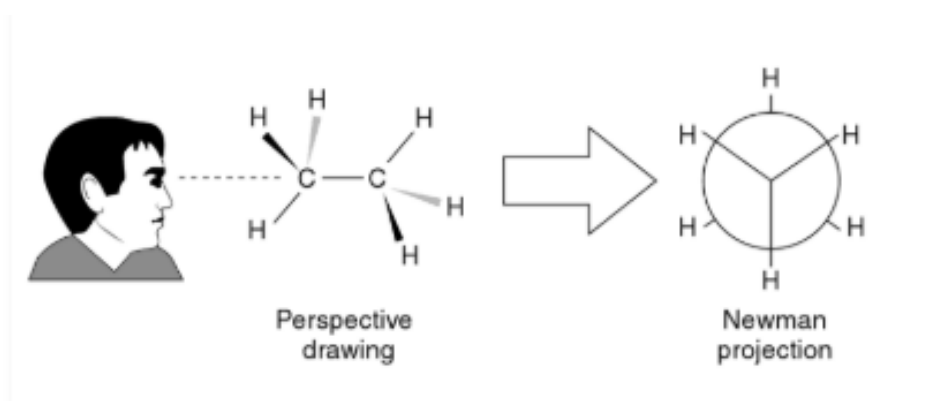
Stereochemistry

Stereochemistry is based on the spatial orientation of atoms attached to a molecule. For bond-line structure, things on non-wedge/dash can be perceived to be flat on the page. Things on wedges can be thought of as coming out of the page, and things on dashes can be thought of as going into the page.



In this image of a 3D Carbon chain, the white atoms represent Hydrogen while black atoms are Carbon and red is Oxygen. Carbon with 4 bonds is sp^3 hybridized and its bonds can be represented with a wedge, dash, and solid line. Here, the Hydrogen atoms that appear to be closer to us would go on a wedge while the ones pointing away from us would be on a dash. All carbons lie flat on the page, and the leftmost Hydrogen would also be flat on the page. The rightmost carbon along with the Oxygen atoms attached to it are all flat on the page (i.e. they shouldn't be drawn on a wedge or dash) because they are all sp^2 hybridized.

Newmann projections are 2D representations of 3D molecules from the perspective that you are looking right at it.



If you look at the front carbon to back carbon, **wedges go on the right side** of the Newmann projection and **dashes go on the left side of the Newmann**. This might be easier to see with the following image:

The two views should look something like this:



Note that when we look from the left, the groups on wedges (orange) end up on the **right**

When we look from the right, the groups on wedges (orange) end up on the **left**

The circle represents the cat's body, since the front and back hips block each other.

Maybe you noticed this helpful correspondence:

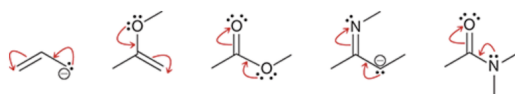
- ◆ When we looked at the cat from the **left** (i.e. front view) the groups on **wedges (orange)** ended up on the **right** side.
- ◆ When we looked at the cat from the **right** (i.e. back view) the groups on **wedges (orange)** ended up on the **left** side

Newmann projections are useful since Carbon-Carbon single bonds can undergo free-rotation, meaning that they can change their spatial orientation relative to the carbon's they are attached to (this will be useful for E2 mechanisms).

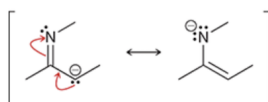
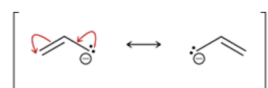
Resonance

For resonance, there are five patterns to look for:

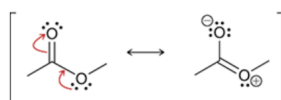
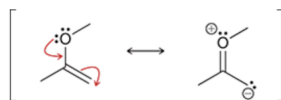
1. Allylic Lone Pairs



Let's carefully consider the formal charges produced in each of the cases above. When the atom with the lone pair has a negative charge, then it transfers its negative charge to the atom that ultimately receives a lone pair:

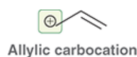


When the atom with the lone pair does not have a negative charge, then it will incur a positive charge, while the atom receiving the lone pair will incur a negative charge:



Lone pairs next to π bonds are called allylic lone pairs. Allylic lone pairs are delocalized thus the atom they reside on has an empty p-orbital, meaning their hybridization is not sp^3 but rather sp^2 or sp.

2. Allylic Carbocation

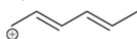


When there is an allylic carbocation, only one curved arrow will be required; this arrow goes from the π bond to form a new π bond:

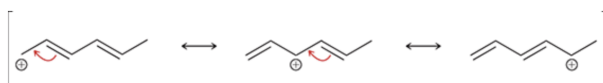


Notice what happens to the formal charge in the process. The positive charge is moved to the other end of the system.

In the previous example, the positive charge was next to one π bond. The following example contains two π bonds, which are said to be **conjugated**, because they are separated from each other by exactly one σ bond (we will explore conjugated π systems in more detail in [Chapter 16](#)).



In this situation, we push each of the double bonds over, one at a time:



A carbocation is sp^2 hybridized thus it has an empty p-orbital that electrons (in the π bond) can fill.

3. Lone Pair Adjacent to Carbocation

3. A lone pair adjacent to C^+ . In the following example, the oxygen atom exhibits three lone pairs, all of which are adjacent to the positive charge. This pattern requires only one curved arrow. The tail of the curved arrow is placed on a lone pair, and the head of the arrow is placed to form a π bond between the lone pair and the positive charge:



Notice what happens with the formal charges. The atom with the lone pair has a negative charge in this case, and therefore the charges end up canceling each other. Let's consider what happens with formal charges when the atom with the lone pair does not bear a negative charge. For example, consider the following:

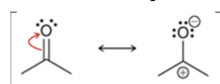


A carbocation is sp^2 hybridized thus it has an empty p-orbital that electrons (from the lone pair) can fill.

4. π Bond Between Two Atoms of Diff. EN



In these situations, we move the π bond up onto the electronegative atom to become a lone pair:



Oxygen is electronegative enough to pull the electrons from the double-bond up making O^- .

5. Conjugated Pi Bonds in a Ring

When conjugated π bonds are enclosed in a ring of alternating double and single bonds, we can push all of the π bonds over by one position:

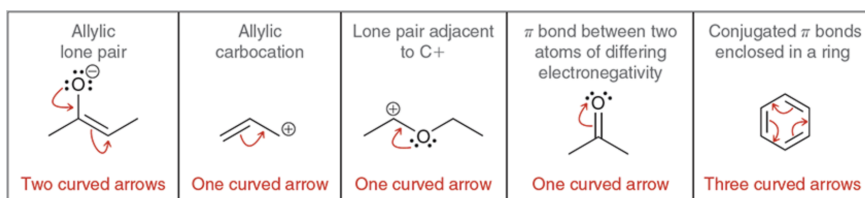


When drawing the resonance structure above, all of the π bonds can be pushed clockwise or they can all be pushed counterclockwise. Either way achieves the same result.

All of the carbon atoms in the ring are sp^2 thus they are able to move the π bonds around as shown here.

Summary

A summary of the different patterns is as follows:



Judging Resonance Stability is based on the Following Order

1. Every atom should have a full octet
2. Fewest formal charges is more significant
3. If there are formal charges, negative charges should go on the more electronegative atoms

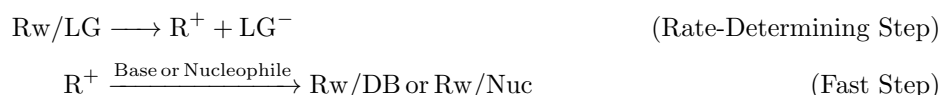
Assess these rules in order! The first point of difference decides the most significant structure. Ex: if A meets 1 and 3 while B meets 2 and 3, A is more significant.

Note that a structure can have a formal charge while still having a complete octet, so be careful!

Substitution & Elimination

SN1/E1 Reactions

The reason these reactions have been grouped together is that they follow the same general pattern with one distinction: whether a nucleophile or base is used. These reactions are called "unimolecular" hence the 1 because their rates only depend on the concentration of one molecule: the species with the leaving group.



In this case, the starting material initially creates a carbocation before a base deprotonates a β Hydrogen to produce a double bond or the nucleophile attacks the C^+ . Since rate is only dependent on the SM slow step, only the alkyl group w/ LG can affect the rate.

Note: Since these reactions proceed through a carbocation, they can only happen on a 2° or 3° species since carbocation stability is as follows: *resonance* > 3° > 2° > 1°

SN2/E2 Reactions

For SN2 and E2, they are bimolecular reactions as their rate is dependent on the alkyl group and base/nucleophile.



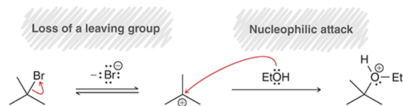
In this case, the formation and "plugging" of the carbocation happens instantaneously so there is only one step. As a result, these are called "concerted" mechanisms.

SN1 & SN2

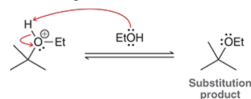
It is important to note that substitution reactions are dependent on kinetics, while **elimination** reactions are dependent on **thermodynamics**. To this extent, steric hindrance plays a large role in determining if substitution will occur. SN2 is the fastest of all mechanisms, so it will want to happen where there is the least steric hindrance (i.e. 1° carbons and CH_4). SN1 is slower since it proceeds through a carbocation, so it requires enough stability to support the C^+ (needs resonance stabilization, 3° , or 2°).

For SN1 Reactions, the general mechanism is as follows:

When a tertiary alkyl halide undergoes ionization in a polar solvent, such as EtOH, the solvent can function as a nucleophile and attack the intermediate carbocation, resulting in a two-step substitution process:

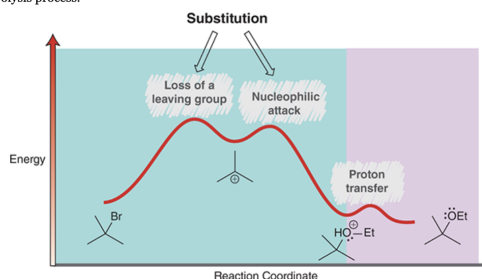


Since a solvent molecule functions as the attacking nucleophile, the process is called *solvolysis*. Notice that the result of this two-step substitution process is an oxonium ion (an intermediate with a positive charge on an oxygen atom). This oxonium ion can then lose its proton to a solvent molecule, giving the observed substitution product:



BY THE WAY

Figure 7.15 shows an energy diagram that depicts all steps in this solvolysis process.



Since S_N1 reactions see the leaving group fully leave before the nucleophile attacks, the nucleophilic attack can occur from either side so there isn't necessarily an inversion of stereochemistry unlike S_N2 (i.e. there is **inversion or retention** of stereochemistry though there is still a slight preference for inversion). Another reason that the nucleophile can attack from either side is that a carbocation is sp^2 hybridized, so it is planar (flat) and can more easily be attacked from either side than an sp^3 hybridized carbon.

For S_N2 Reactions, the general mechanism is as follows:

THE S_N2 MECHANISM



As previously mentioned, S_N2 reactions occur all in one step so they are more sensitive to steric conditions. The carbocation formation and attack of a nucleophile essentially happen at the same time so S_N2 doesn't need to worry about stability like S_N1 . Instead, it wants the least steric hindrance as possible so it prefers to happen at methyl (CH_3LG methyl with a LG instead of 4th hydrogen), 1° , and occasionally 2° carbons.



The reactant exhibits the *R* configuration, while the product exhibits the *S* configuration. That is, this reaction is said to proceed with **inversion of configuration**. This stereochemical outcome is often called a Walden inversion, named after Paul Walden, the German chemist who first observed it. The requirement for inversion of configuration means that the nucleophile can only attack from the back side (the side opposite the leaving group) and never from the front side (Figure 7.2). There are two ways to explain why the reaction proceeds through **back-side attack**:

1. The lone pairs of the leaving group create regions of high electron density that effectively block the front side of the substrate, so the nucleophile can only approach from the back side.
2. Molecular orbital (MO) theory provides a more sophisticated answer. Recall that molecular orbitals are associated with the entire molecule (as opposed to atomic orbitals, which are associated with individual atoms). According to MO theory, the electron density flows from the HOMO of the nucleophile into the LUMO of the electrophile. [LOOKING BACK](#) As an example let's focus our attention on the LUMO of methyl bromide (Figure 7.3).



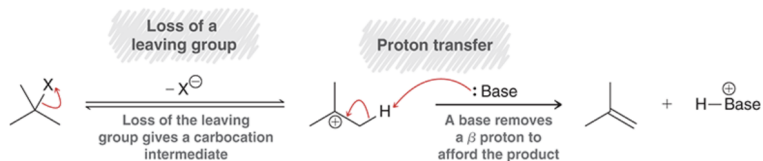
This graphic is a bit excessive but in essence, **S_N2** results in the **inversion of stereochemistry** if the LG is on a chiral center. The reason for this is the nucleophile attacks at the same time that the LG leaves. Since each group has electrons, electron-electron repulsion (which is what steric hindrance really is) will mean it is less favorable to attack on the same side that the LG leaves on.

E1 & E2

Unlike substitution reactions, elimination reactions are based in thermodynamics, thus they care less about sterics and more about electronic effects. This can be seen since the Zaitsev product (double bond with more carbons connected to it) is preferred over Hofmann (double bond with fewer carbons connected) since the Zaitsev product is more energetically favorable. Both of these mechanisms require there to be a $\beta-H$ that can be deprotonated to create a double bond between the α and β carbon to work.

For E1 Reactions, the general mechanism is as follows:

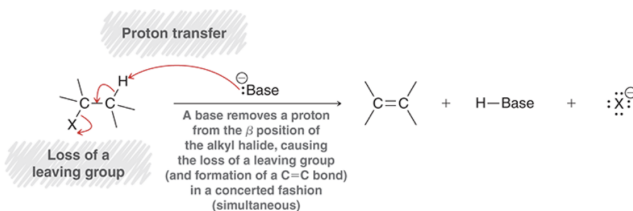
MECHANISM 7.4
THE E1 MECHANISM



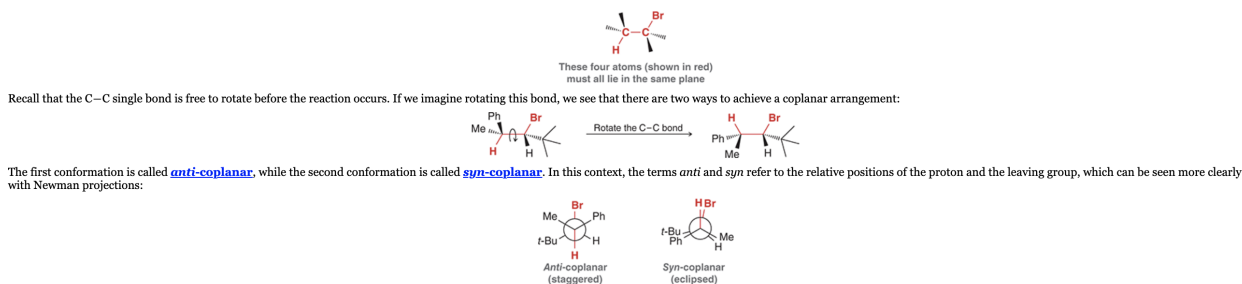
Like $\text{S}_{\text{N}}1$, E1 mechanisms create a full carbocation before occurring. As a result of this, they require a higher substituted substrate (3°) in order to be sufficiently stable to proceed. Because the E1 mechanism doesn't require the β -H to be anti-periplanar ($\sim 180^\circ$ apart) from the LG, **E1 elimination always results in the Zaitsev product**.

For E2 Reactions, the general mechanism is as follows:

THE E2 MECHANISM

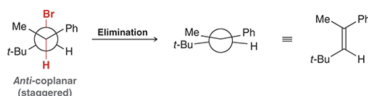


In this case, no carbocation is directly formed but it is still necessary to have a β -H. Furthermore, the E2 mechanism requires that the β -H be 180° apart from the LG in order to proceed, so it might be necessary to rotate your bond via a Newmann projection.



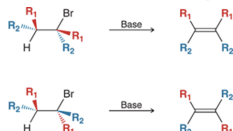
LOOKING BACK

When viewed in this way, we can see that the *anti-coplanar* conformation is staggered, while the *syn-coplanar* conformation is eclipsed. Elimination via the *syn-coplanar* conformation would involve a transition state of higher energy as a result of the eclipsed geometry. Therefore, elimination occurs more rapidly via the *anti-coplanar* conformation. In fact, in most cases, elimination is observed to occur exclusively via the *anti-coplanar* conformation, which leads to one specific stereoisomeric product:



The requirement for coplanarity is not entirely absolute. That is, small deviations from coplanarity can be tolerated. If the dihedral angle between the proton and the leaving group is not exactly 180° , the reaction can still proceed as long as the dihedral angle is close to 180° . The term **periplanar** (rather than coplanar) is used to describe a situation in which the proton and leaving group are *nearly* coplanar (for example, a dihedral angle of 178° or 179°). In such a conformation, the orbital overlap is significant enough for an E2 reaction to occur. Therefore, it is not absolutely necessary for the proton and the leaving group to be *anti-coplanar*. Rather, it is sufficient for the proton and the leaving group to be **anti-periplanar**. From now on, we will use the term *anti-periplanar* when referring to the stereochemical requirement for an E2 process.

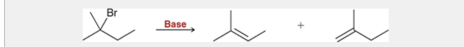
The requirement for an *anti-periplanar* arrangement will determine the stereoisomerism of the product. In other words, the **stereoisomeric product of an E2 process depends on the configuration of the starting alkyl halide**:






The image above shows how one might proceed with the rotation. Having the β -H is necessary, so the location of the other substituents may change in order to accomplish this necessity.

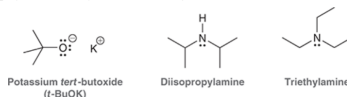
Zaitsev vs. Hofmann

TABLE 7.3
PRODUCT DISTRIBUTION OF AN E₂ REACTION AS A FUNCTION OF BASE



BASE	ZAITSEV	HOFMANN
	71%	29%
	28%	72%
	8%	92%

When ethoxide is used, the Zaitsev product is the major product. But when sterically hindered bases are used, the Hofmann product becomes the major product. This case illustrates a critical concept: *The regiochemical outcome of an E₂ reaction can often be controlled by carefully choosing the base.* Sterically hindered bases are employed in a variety of reactions, not just elimination, so it is useful to recognize a few sterically hindered bases.



Note that while the Zaitsev product will always be more favorable, a strong, sterically hindered base causing a substrate to go through E₂ will produce the Hofmann product.

Summary

A summary for the different substrates (substitution of α Carbon) and the reactants are as follows:

	Strong base Weak nucleophile	Strong base Strong nucleophile	Weak base Strong nucleophile	Weak base Weak nucleophile
1°	E2	E2 S _N 2	S _N 2	
2°	E2	E2 S _N 2	S _N 2	
3°	E2	E2	S _N 1	S _N 1 E1

In this case, the major product will be whatever forms in the greater amount since some combinations can result in two different species.

Strong base weak nucleophile: DBN, DBU

Strong base strong nucleophile: HO⁻, MeO⁻, EtO⁻

Weak base strong nucleophile: I⁻, Br⁻, Cl⁻, RS⁻, HS⁻, RSH, H₂S

Weak base weak nucleophile: H₂O, MeOH, EtOH

Nucleophilicity vs. Basicity

“Good” nucleophiles are fast; “good” bases are strong. This distinction is made since kinetics is irrelevant to elimination and thermo is irrelevant to substitution.

What makes a good nucleophile/base is as follows:

Negative charges

Larger atoms housing the lone pairs are more polarizable (they can shift their charge around easier) so they can be used to attack/deprotonate more readily (Sulfur is very large and therefore polarizable so it's a good nucleophile even when neutral)

Where base trends differ from nucleophilic trends is in sterics. A larger atom is less likely to behave as a nucleophile and more likely to act as a base.