Chapters 6 through 8. Substitution and Elimination Reactions.

7.1. Definitions.

In an acid-base reaction such as $CH_3CO_2H + NH_3 \rightarrow CH_3CO_2^- + NH_4^+$, the N acts as a *nucleophile* (Greek for "loving the nucleus), the H acts as an *electrophile* ("loves electrons"), and the O that accepts the pair of electrons acts as a *leaving group*. The acid-base reaction is the simplest model for a *substitution* reaction, which is a reaction in which a σ bond between atom 1 and atom 2 is replaced by a σ bond between atom 1 and atom 3. Substitution reactions are incredibly important in organic chemistry, and the most important of these involve substitutions at C. For example:



This substitution reaction, discovered in 1849, involves the *nucleophilic* O making a new bond to the *electrophilic* C, and the bond between the electrophilic C and the *leaving group* I breaking.

Any Brønsted base can also act as a nucleophile, and any nucleophile can also act as a Brønsted base, but some compounds are particularly good bases and particularly poor nucleophiles, whereas some are particularly poor bases and particularly good nucleophiles. Any Brønsted or Lewis acid can also act as an electrophile, but there are many electrophiles that are neither Brønsted nor Lewis acids (as in the example above).

A haloalkane, e.g. CH₃CH₂Br, can in principle undergo either of two polar reactions when it encounters a lone pair nucleophile, e.g. MeO⁻. First, MeO⁻ might *replace* Br⁻ at the electrophilic C atom, forming a new C–O bond and giving an ether as the product. This is *substitution*, because the C–Br σ bond is replaced with a C–O σ bond. Second, MeO⁻ might attack a H atom that is *adjacent* to the electrophilic C atom, giving MeOH, Br⁻, and an alkene as products. The electrons in the C–H bond move to form the π bond, and the electrons in the C–X bond leave with X⁻. This is *elimination*, because a new π bond is formed, and because the elements of the organic starting material are now divided between more than one product. Elimination requires that the substrate have a C–X bond *and* adjacent C–H bonds, while substitution requires only that the substrate have a C–X bond.





A reaction involves the formation and cleavage of bonds. A mechanism is a story we tell about the changes in the arrangement of the electrons in the starting materials that led to products. When multiple bonds are made or broken, they are usually not made and broken all at one time. A mechanism describes the order in which the different bonds are made and broken and which electrons moved to break and form particular bonds. A mechanism can also help us generate hypotheses about the rate and stereochemical results of a reaction that we can then use to test whether our story about how the reaction occurred is correct.

We will see soon that there are two mechanisms by which nucleophilic substitution at $C(sp^3)$ most often occurs, and there are two mechanisms by which elimination from $C(sp^3)$ most often occurs. The purpose of this chapter is to learn how the reaction conditions and the structures of the Lewis base and the substrate affect the relative rates of the different possible reaction pathways.

Substitution and elimination reactions can occur under either basic or acidic conditions. The reactions have very different characteristics under basic or acidic conditions, so we'll discuss them separately.

7.2. Electrophiles.

All substitution and elimination reactions require an electrophile that contains a leaving group. The most common such electrophile is a haloalkane, RX, where the leaving group is halide, X^- , or an alcohol, where the leaving group is ^-OH .

Different halides have different *leaving group abilities*. The leaving group ability of X^- is determined by two factors.

• The *strength* of the C-X bond. The weaker the bond, the better the leaving group. The strength of the bond depends on the amount of orbital overlap between C and X. C is a small element, so the overlap decreases as the size of X increases, i.e. F > Cl >> Br >> I.

• The *polarization* of the C–X bond. The more polarized the bond, the better the leaving group. The bond polarization decreases with decreasing electronegativity of X, in the order F > Cl > Br >> I.





The actual order of leaving group ability is $I^- > Br^- > Cl^- >> F^-$. In fact, alkyl fluorides are nearly inert to substitution or elimination (hence the stability of Teflon).

Other electronegative groups, e.g. RO⁻, can also act as leaving groups in principle. Comparing F⁻ and HO⁻, both are about the same size, but F⁻ is more electronegative. So we can conclude that HO⁻ is a worse leaving group than F⁻. Since F⁻ is already a very bad leaving group, HO⁻ must be a *really* bad leaving group. HO⁻ usually leaves only when the mechanism is E1cb, which we won't discuss, or when extremely harsh conditions are used (i.e., 50% aq. KOH).

Replacing the H in HO⁻ with more electronegative groups, however, increases the leaving group ability. When H is replaced with $RS(O)_2$, one obtains a very important class of leaving groups, the *sulfonate esters*. The most common sulfonates, RSO_3^- , are tosylate (short for toluenesulfonate, -OTs) and mesylate (short for methanesulfonate, -OMs). Tosylates and mesylates are easily made from alcohols, a sulfonyl chloride such as tosyl chloride TsCl or mesyl chloride MsCl, and a base to neutralize the byproduct HCl. The O of the alcohol acts as a nucleophile toward electrophilic S, displacing the leaving group Cl⁻ by an S_N2 substitution reaction.



The conversion of an alcohol to a tosylate represents a way of turning a lousy leaving group, \neg OH, into a good leaving group, \neg OTs (leaving group ability \approx Br \neg). Tosylates are sometimes called *pseudohalides*, because their properties are similar to the halides. From now on, whenever we say halides, we are also referring to tosylates and mesylates.

Another way of converting the lousy leaving group HO^- into a good leaving group is to convert OH to Br. The most convenient way of accomplishing this transformation is to use the reagent PBr₃. We'll talk later about how this reagent works, but for right now, all you need to know is that the purpose in life of PBr₃ is to convert OH into Br.



Yet another way of converting the lousy leaving group HO⁻ into a good leaving group is to protonate it. This makes it into the pretty good leaving group OH_2 (leaving group ability $\approx Cl^-$). Alcohols ROH are weak bases, with pK_a of their conjugate acids $ROH_2^+ \approx 0$, so an alcohol ROH is only protonated under acidic conditions to give ROH_2^+ , an electrophile with a pretty good leaving group. This process does not occur under basic conditions. *Alcohols (and ethers) are electrophiles under acidic conditions, but not under basic conditions*.

7.3. Nucleophiles.

A nucleophile is a compound that has a relatively high energy pair of electrons that is available to react with an electrophile. In other words, any Brønsted base is also a nucleophile. In this chapter we will be talking about substitutions at $C(sp^3)$ electrophiles, and in these cases the nucleophile is generally either a metal salt (KOH, NaNH₂, EtSK, CH₃CH₂CH₂CH₂ONa, NaBr), in which case the reactive pair of electrons comes from the bond between the metal and nonmetal, or a neutral compound with a lone pair (R₃N, H₂O, ROH, RCO₂H, R₂S, R₃P). Remember that a metal salt such as KBr is dissociated into two ions, K⁺ and Br⁻, and the latter is the species that acts as a nucleophile. Sometimes we do not draw the counterion associated with the anionic nucleophile.

All nucleophiles are also Brønsted bases, but they may be strong bases or weak bases. Only weak bases can exist under acidic conditions, so under acidic conditions the nucleophiles we tend to see are weak bases only. This means either they are neutral (H_2O , MeOH, CH_3COOH) or they are anionic, heavier halides (Cl^- , Br^- , or I^-). Under basic conditions, though, any nucleophile can exist. A neutral nucleophile under basic conditions is often deprotonated by the base that is present before reacting with the electrophile.

7.4. Drawing Substitution and Elimination Products.

Before we discuss the mechanisms of substitution and elimination reactions, it's best for us first to learn how to draw the products of such reactions. The methods outlined below apply regardless of whether the conditions are acidic or basic. Please note that these methods for drawing products are not intended to reflect the mechanisms by which these reactions occur. They are simply intended to aid you in drawing the product.

Regardless of whether you are drawing a substitution or elimination product, you must first identify the electrophilic atom. In this chapter, the electrophilic atom will always be C. The electrophilic C atom is attached to a leaving group. The leaving group is usually Cl, Br, or I, but it may also be a sulfonate such as OTs or OMs or even an ammonio group such as $-NMe_3$. If the conditions are acidic, OH or OC(=O)R (e.g., AcO) may act as a leaving group.

After identifying the electrophilic atom, to draw the substitution product:

1. Identify the nucleophilic atom.

(a) Look for a nonmetal that is attached to a metal, such as EtSNa, KOH, or HC=CNa; the nonmetal is the nucleophilic atom.

(b) Failing that, look for an anionic atom, such as MeO^- , $-NH_2$, or -CN.

(c) Failing that, look for a neutral atom that bears an acidic H atom, especially if it is the solvent or the conditions are basic. (E.g., NH_3 , HBr, HCl, H_2O , EtOH, RSH, RCO_2H such as AcOH, RC=CH, and a C atom adjacent to a C=O group.)

(d) Failing that, look for a neutral atom that has a lone pair, such as $EtNH_2$, Ph_3P , or H_2O .

2. If the nucleophilic atom is *neutral* and is attached to a metal or at least one H atom, erase the metal or *one* H atom and reduce the charge of the nucleophilic atom by 1.

3. Replace the C-leaving group bond with a bond between the same C and the nucleophilic atom. The leaving group decreases its formal charge by 1, and the nucleophilic atom increases its formal charge by 1 (even if you just decreased it).

After identifying the electrophilic atom, to draw the elimination product:

1. Identify a C atom that is attached to the electrophilic C atom and that bears a H atom. (In general, the H-bearing atom may be an element other than C, but, in this chapter, we will only be dealing with the case where it is C.)

(a) If more than one kind of C atom attached to the electrophilic one bears a H atom, then more than one elimination product can be drawn.

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(b) If no C atom attached to the electrophilic one bears a H atom, then an elimination product cannot be drawn.

- 2. Break the bond between the electrophilic C atom and the leaving group.
- 3. Break the bond between the adjacent C atom and its H atom.
- 4. Draw an additional π bond between the two C atoms of the previous two steps.

7.5. Substitution and Elimination Mechanisms. Acidic and Basic Conditions.

Substitution requires one bond to break and another to be made. We can imagine three different ways (mechanisms) by which this reaction might proceed.

- 1. The nucleophile comes in at the same time as the leaving group leaves.
- 2. The leaving group leaves, then the nucleophile comes in.
- 3. The nucleophile comes in, then the leaving group leaves.

The third mechanism requires a 10-electron C intermediate, so it doesn't occur at electrophilic $C(sp^3)$ atoms. The first two mechanisms are called the S_N^2 and S_N^1 mechanisms.

Note the curved arrows that I use to show how bonds make and break in these reactions. The electronflow arrows show the movement of *electrons*, just like they did when we used them to draw resonance structures. In the S_N^2 example, a lone pair (here represented by the negative charge, although a nucleophile can be uncharged as well) that is currently residing on the nucleophilic atom moves to form a bond to the electrophilic C atom. But that C atom already has an octet, so it cannot accept a new pair of electrons unless it sheds a pair of electrons. That pair is the pair in the C–Br bonds, and those electrons become a lone pair on the Br atom after it leaves.

Elimination requires two bonds, C–H and C–X, to break. We can imagine three different ways (mechanisms) by which this reaction might proceed.

- 1. Both bonds might break simultaneously.
- 2. The C–X bond might break first.

3. The C–H bond might break first.

The first mechanism is called E2, the second is called E1, and the third is called E1cb. We won't talk about E1cb in this chapter, but you'll learn about it when you learn about aldol reactions. (The dehydration step that often follows an aldol reaction is an elimination of H_2O that proceeds by the E1cb mechanism.)



The S_N1 and E1 mechanisms form an intermediate with an electron-deficient, cationic C atom. This C atom wants to regain its octet, so it is a very strong electron acceptor — in other words, a Lewis acid. Acids cannot be generated spontaneously under basic conditions, so *the* S_N1 and E1 mechanisms can occur only under acidic conditions.

The E2 mechanism has the C–H bond breaking at the same time as the C–X bond is breaking. The pK_a of the C–H bond is in the 40's. Now, a base *that* strong is not required to deprotonate the C atom — a full negative charge never develops on the C atom, because the electrons from the C–H bond, rather than going to the C atom, instead are used to make a π bond to the electrophilic C atom — but nevertheless, a good base is required to promote the reaction. *E2 mechanisms can occur only under basic conditions*.

The S_N^2 mechanism requires that the nucleophile attack a C atom that already has its octet. As a result, the nucleophile needs to be a pretty good one. Many nucleophiles are also decent bases, and many nucleophiles (e.g., ROH) are made into much better nucleophiles by deprotonating them (e.g., to give RO⁻), so S_N^2 mechanisms usually occur under basic conditions. However, some very good nucleophiles (Br⁻, I⁻) are very poor bases, so S_N^2 mechanisms can occasionally occur under acidic conditions.

The mechanism, stereochemical outcome, and even product of a substitution or elimination reaction depend on whether the reaction conditions are acidic, basic, or neutral. How do you identify the nature of the reaction conditions?

• If an acid is present, the conditions are acidic. Sometimes we don't specify the acid, just writing H⁺. Otherwise, look for mineral acids such as HCl, HBr, or H₂SO₄, carboxylic acids (RCO₂H) such as acetic acid (AcOH), and sulfonic acids (RSO₃H) such as toluenesulfonic acid (TsOH) and methanesulfonic acid (MsOH). Ammonium salts such as NH_4^+ Cl⁻ and pyrH⁺ TsO⁻ (pyr = pyridine) are also acids. *Water and alcohols do not count as acids for the purposes of defining whether the conditions are acidic or basic*.

• If a base is present, the conditions are basic. Look for anions such as HO^- , F^- , and MeS^- . Look for alkali-metal and alkaline-earth salts such as BuLi, PhMgBr, NaNH₂, LiN(*i*-Pr)₂ (LDA), *t*-BuOK, and NaHCO₃. (You may find salts of the heavier halogens such as NaCl, KBr, and NaI under acidic conditions, but if no acid is present, you can consider the conditions basic.) Also look for amines such as NH₃, Et₃N, and EtN(*i*-Pr)₂, which are pretty good bases.

• If no acid or base is present, but the electrophile is a secondary or tertiary halide, then the conditions are "stealth acidic". Although no acid or base is present at the beginning of the reaction, as the substitution or elimination reaction proceeds, acid is generated. For example, when EtOH reacts with Me₃CCl in a substitution reaction, the products are Me₃COEt and HCl. We'll soon discuss why a secondary or tertiary halide is required for "stealth acidic" conditions.

 \circ If no acid or base is present, but the nucleophile contains a neutral, heavy, lone-pair-bearing nonmetal such as in Ph₃P or Me₂S, you can consider the conditions to be basic.

7.6. Substitution and Elimination under Basic Conditions.

7.6.1. The S_N2 Mechanism for Substitution.

In the S_N^2 mechanism, the nucleophile attacks the electrophilic C atom directly. As the nucleophile comes in, the C atom begins to acquire more than eight electrons, so the bond to the leaving group breaks simultaneously. In the TS, the C atom is partially bound to both the nucleophile and the leaving group. The nucleophile continues to come in and the leaving group continues to leave, until finally the product has been obtained.

$$Nu^{-} \xrightarrow{\delta^{-}} Br \xrightarrow{\delta^{-}} Nu^{-} Br \xrightarrow{\delta^{-}} Nu^{-} Br \xrightarrow{\delta^{-}} Br \xrightarrow{\delta^{-}$$

This mechanism has no intermediates. Because of this, the rate-determining step is bimolecular; that is, the rate of the reaction is described by the following equation.

Grossman, CHE 230 rate = k [Nu⁻] [alkyl halide]

In other words, the rate of the reaction is proportional to *both* the concentration of the nucleophile *and* the concentration of the organic substrate. If one halves the concentration of nucleophile, the rate of the reaction should halve as well. This mechanism is called $S_N 2$, for substitution–nucleophilic–bimolecular.

We can draw a reaction coordinate diagram for the S_N^2 reaction. A reaction coordinate diagram is a way of showing the energy of the system as it moves from starting materials through the transition state to the products. The S_N^2 substitution reaction has a particularly simple reaction coordinate diagram: starting materials, a single transition state, and products.

Some typical $S_N 2$ substitution reactions:

 $\begin{array}{l} \mathrm{HO^{-}} + \mathrm{CH_{3}I} \rightarrow \mathrm{HOCH_{3}} + \mathrm{I^{-}} \\ \mathrm{EtS^{-}} + \mathrm{CH_{3}CHClCH_{3}} \rightarrow \mathrm{CH_{3}CH(SEt)CH_{3}} + \mathrm{Cl^{-}} \\ \mathrm{Et_{3}N} + \mathrm{PhCH_{2}Br} \rightarrow \mathrm{Et_{3}}^{+} \mathrm{NCH_{2}Ph} \ \mathrm{Br^{-}} \\ \mathrm{KOAc} + \mathrm{bromocyclohexane} \rightarrow \mathrm{cyclohexyl} \ \mathrm{acetate} + \mathrm{KBr} \\ \mathrm{BuNH_{2}} + \mathrm{CH_{3}CH_{2}CH(OTs)CH_{3}} \rightarrow \mathrm{CH_{3}CH_{2}CH(}^{+} \mathrm{NH_{2}Bu)CH_{3}} \ \mathrm{Br^{-}} \\ & \left[\mathrm{after} \ \mathrm{workup}, \mathrm{CH_{3}CH_{2}CH(\mathrm{NHBu})CH_{3} \right] \\ \mathrm{EtOH} + \mathrm{BuBr} + \mathrm{base^{-}} \rightarrow \mathrm{EtOBu} + \mathrm{base^{-}H} + \mathrm{Br^{-}} \\ & \mathrm{PhC=CH} + \mathrm{BuLi}, \ \mathrm{then} \ \mathrm{CH_{3}I} \rightarrow \mathrm{PhC=CCH_{3}} + \mathrm{LiI} + \mathrm{BuH} \end{array}$

Note that the electrophile C in every example has at least one H attached; that is, the alkyl group in the alkyl halide is either Me, primary (1°, two H's), or secondary (2°, one H), but never tertiary (3°, no H's). The last phenomenon is due to steric hindrance of the $S_N 2$ substitution reaction. In the $S_N 2$ mechanism the substrate goes from a four-coordinate C in the starting material to a very crowded five-coordinate C in the TS, so the reaction is very sensitive to steric hindrance about the electrophilic C. Tertiary alkyl halides do not undergo $S_N 2$ substitution reactions!

Also note that nucleophiles can be neutral or anionic. In the last two entries, the nucleophile is initially neutral, but it is deprotonated by the base in the mixture to give an anion that cats as the nucleophile.

Some notes on conventions. I've written out the nonorganic products in all cases, but in fact we often omit the nonorganic products. The fourth entry shows that a lone-pair-bearing nucleophile with an acidic H can lose that H after the substitution reaction to regenerate a neutral compound; we often omit the intermediate charged product and simply draw the neutral one. Also, sometimes we write the nucleophile above the arrow, and sometimes we write the solvent above the arrow, and sometimes we write the arrow.

When we draw a mechanism for an $S_N 2$ substitution reaction, we indicate the movement of electrons with curved arrows. If the nucleophile has an acidic H atom that can be removed under the basic conditions, the H atom is removed first, and then the conjugate base attacks the electrophilic C.



Sometimes the base is added to the nucleophile first, in a separate step, before the electrophile is added.

Reaction:



Mechanism:



You may have noticed that I drew the intermediate nucleophile in the reaction above with a lone pair and negative charge on C, even though the lower energy resonance structure has them on O. It matters not one whit which resonance structure you draw for your intermediates. It is equally acceptable to drw the O⁻ resonance structure, as shown:



Note: A mechanism is a story we tell about how a reaction proceeded from starting materials to products. *To draw a mechanism, you must know the starting materials, the reaction conditions, and the products.*

So far we have talked only about intermolecular substitutions, that is, reactions in which one molecule, a nucleophile, reacts with another molecule, an electrophile, to give the product. Suppose, however, that both the nucleophile and electrophile were contained in the same molecule. What then? In that case, one can still get a substitution reaction, but the product is now cyclic, rather than acyclic. Rings of all sizes can be formed this way, although most often three-, five-, and six-membered rings are formed. The latter two are formed because the reactive ends are not too far apart that they won't meet up with one another now and again (not too unfavorable entropy) and because the products are not very strained (favorable enthalpy); three-membered rings are formed easily because the ends are so close together that it is very likely that they will meet up with one another and react (favorable entropy), even though the product is very strained (unfavorable enthalpy). Rings larger than six are harder to prepare because of worse entropy.



7.6.2. Stereochemistry of the S_N2 Mechanism.

Let's look at the stereochemistry of the S_N^2 reaction. Suppose we have a haloalkane in which the electrophilic C atom is stereogenic, e.g., *sec*-butyl bromide, and suppose further that we have a sample of this compound in which that atom is configurationally pure. The starting material is chiral, the transition state is chiral, and the product is chiral, so we would predict that the product is configurationally pure also. This is found to be true for nucleophilic substitutions that proceed by the S_N^2 mechanism. (This is as long as the nucleophile is not identical to the leaving group. If Nu = Br, then the transition state has a plane of symmetry and is achiral.) We can see, though, that the configuration of the stereocenter in the product is *inverted* with respect to the configuration in the starting material. For example, if we start off with (*R*)-2-bromobutane, and if the incoming nucleophile has the same CIP priority as the leaving group, then the product has the absolute (*S*) configuration.

call this the *Walden inversion*. (Don't confuse this inversion with the lone pair inversion that occurs so easily in amines.) It may help to visualize the inversion starting from the transition state. The transition state wants to collapse to a tetrahedral ground state. It can do that by expelling Nu⁻ and having the three equatorial groups move to the left (giving starting material), or it can do it by expelling Br⁻ and having the three equatorial groups move to the right (giving product). In one direction the C atom assumes one configuration, and in the other direction it assumes the opposite configuration. To sum up, *when a substrate undergoes nucleophilic substitution by the* S_N2 *mechanism at a stereocenter that is configurationally pure, the stereocenter in the product is configurationally pure and inverted with respect to the starting material*.

$$\begin{array}{c} H_{3}CH_{2}C_{+}^{CH_{3}} \\ H_{-}^{CH_{2}} \\ H_{-}^{CH_{3}} \\ H_{-}^{-} \\ H_{-}^{-$$

When an alcohol is converted into a tosylate, the C–O bond is not affected, so the configuration of the electrophilic C remains unchanged. However, when an alcohol is converted into a bromide with PBr₃, the C–O bond is replaced by a C–Br bond by an S_N^2 process, so the configuration of the electrophilic C is inverted. (Actually, the mechanism by which an alcohol is converted to a bromide with PBr₃ consists of two S_N^2 reactions. In the first, the O of ROH is the nucleophile, the P of PBr₃ is the electrophile, Br⁻ is the leaving group, and ROPBr₂ is obtained. In the second, the Br⁻ produced in the first step is the nucleophile, ROPBr₂ is the electrophile, \neg OPBr₂ is the leaving group, and RBr is obtained. But the alcohol C is affected only by in step 2, so it undergoes clean inversion.)



7.6.3. The E2 Mechanism for Elimination.

In the E2 mechanism, a base attacks a H atom bound to C next to the electrophilic C. (B⁻ here is the base, not boron. The base might or might not be charged.) As the base forms its bond to H, the electrons in the C–H bond must leave H and find somewhere else to go. They move to form a π bond to the electrophilic C next door. The electrophilic C next door, though, has an octet, so at the same time as the π bond forms, the C–X bond must break. In the end, the base has been protonated, X⁻ has left, and an alkene has been formed.



This mechanism, like the S_N^2 mechanism, has no intermediates. The rate-determining step is bimolecular; that is, the rate of the reaction is described by the following equation.

rate = $k [B^{-}]$ [alkyl halide]

(The bimolecularity of the rate-determining step provides the "2" in "E2"). The rate of the reaction is proportional to *both* the concentration of the base *and* the concentration of the organic substrate.

The E2 mechanism requires that a strong base be available to pull the H off the C adjacent to the electrophilic C. Strong bases cannot exist under acidic conditions. Therefore, *the E2 mechanism occurs only under basic conditions*. However, any kind of alkyl halide $(1^\circ, 2^\circ, 3^\circ)$ can undergo E2 elimination, as long as there is a C–H bond adjacent to the leaving group. CH₃X and PhCH₂X electrophiles cannot undergo E2 elimination. Examples of E2 eliminations:

 $t-BuO^- + CH_3CH_2I \rightarrow CH_2=CH_2 + t-BuOH + I^-$ KOH + bromocyclohexane \rightarrow cyclohexene + KBr Et₃N + PhCH₂CH₂OTs \rightarrow PhCH=CH₂ + Et₃NH TsO⁻ EtO⁻ + 1-methyl-1-chlorocyclopentane \rightarrow 1-methylcyclopentene + EtOH + Cl⁻

7.6.4. Zaitsev's Rule. Stereochemistry of the E2 Mechanism.

Suppose you carry out an elimination reaction (E1 or E2) with $CH_3CHBrCH_2CH_3$. You can get three different products: 1-butene, *cis*-2-butene, or *trans*-2-butene. Which one will be the major product? *Zaitsev's rule holds that the major product will be the compound that is lowest in energy*. It happens that the more non-H substituents an alkene has, the lower in energy it is. So 2-butene is lower in energy than 1-butene. We have also seen that *trans*-2-butene is lower in energy than the cis isomer. So the major product is expected to be *trans*-2-butene.

Why does Zaitsev's rule hold? It is because in the TS for the product-determining step (loss of H from the C next to the electrophilic center), the C=C π bond is already beginning to form, so all the factors that cause one alkene to be more stable than another alkene are operating in the TS.

Zaitsev's rule is not an absolute one. The anti-Zaitsev product (called the Hofmann product) is often obtained in smaller or larger proportions. The anti-Zaitsev product tends to be obtained more when the base is very hindered and when the leaving group is a poor one, such as F⁻, ⁻OH, and NMe₃.

Furthermore, Zaitsev's rule cannot be used to predict the stereoisomer (E or Z) that will be obtained from an E2 elimination when both the electrophilic C and the adjacent C are stereogenic. *The E2 elimination reaction almost always occurs from the conformer in which the C–H bond is anti to the C– Br bond*. The reason for this *antiperiplanar* arrangement is to achieve maximum overlap between the developing p orbitals on each C atom in the transition state. Let's look at E2 elimination from the diastereomers of (1-bromo-2-methylbutyl)benzene. The 1S,2S diastereomer gives the Z product, while the 1S,2R diastereomer gives the E product. In other words, elimination that occurs by the E2 mechanism is *stereospecific*.



The antiperiplanar requirement for E2 elimination can be illustrated by looking at elimination reactions in cyclohexyl halides. In cyclohexanes, equatorial C–X bonds are not periplanar to any C–H bonds. Axial C–X bonds, on the other hand, are anti periplanar to neighboring axial C–H bonds. When elimination occurs from a cyclohexane ring by the E2 mechanism, the ring must first assume a conformation in which the C–X group is axial. Compare the rates and products of elimination from menthyl chloride and its diastereomer neomenthyl chloride via the E2 mechanism. The lowest energy conformer of menthyl chloride has all the groups equatorial. Before base-induced elimination can occur, it must assume the high-energy all-axial conformation. In this conformation, only one C–H bond is anti to the C–Cl bond, so only one product is obtained. In neomenthyl chloride, however, the lowest energy conformer has the C–Cl bond axial. Two of the adjacent C–H bonds are axial, so elimination from neomenthyl chloride is 200 times more rapid than elimination from menthyl chloride, because neomenthyl chloride is 200 times more rapid than elimination from menthyl chloride, because neomenthyl chloride does not have to assume a high-energy conformation before elimination can occur.



To determine whether Zaitsev's rule is followed, follow these instructions.

1. Identify the electrophilic atom.

2. Identify every C atom adjacent to the electrophilic one that bears a H atom.

3. If more than one C atom adjacent to the electrophilic one bears a H atom, choose the one that has the fewest H atoms.

4. If both the electrophilic C atom and the H-bearing C atom are stereogenic, determine whether the H that is to be removed and the leaving group can achieve an anti conformation.

(a) If they can, draw the elimination product that follows from that conformation.

(b) If they can't, go to the H-bearing C atom with the next fewest number of acidic H atoms, and repeat.

7.6.5. Predicting Substitution vs. Elimination under Basic Conditions.

Basic conditions are identified by the presence of bonds between metals and nonmetals. The classic example of a base is NaOH, in which there is a bond between a metal (Na) and a nonmetal (O). We have already seen that $S_N 1$ substitutions and E1 eliminations can occur only under acidic conditions. Therefore, *under basic conditions, any substitution at C(sp³) must occur by an S_N2 mechanism, and any elimination must occur by an E2 mechanism.*

Whether substitution or elimination occurs often depends on the relative *basicity* and *nucleophilicity* of the base/ nucleophile. Why shouldn't all good bases be good nucleophiles, too? After all, both require a high-energy pair of electrons. Both bases and nucleophiles react with electrophiles, but basicity measures the ability of a lone pair-bearing atom to attack H⁺ or H–X, whereas nucleophilicity measures the ability of a lone pair-bearing atom to attack electrophilic C–X, e.g. CH₃Br. The different natures of H⁺ (cationic, electron-deficient, very small, unhindered) and CH₃Br (neutral, electron-saturated, bigger,

more hindered) mean that the reactions have slightly different preferences for the nature of the nucleophilic atom.

Basicity: Equilibrium constant of:

 $Nu^- + H^+ \implies Nu-H$

Nucleophilicity: Rate of:

		Nu ⁻	+ CH ₃	\leftarrow CH ₃ Br \longrightarrow		CH ₃ Nu + Br [−]			
Nu:	-SH	-CN	I-	MeO-	HO-	Cl-	NH ₃	H ₂ O:	
Rel. rate:	125	125	100	25	16	1.0	0.7	0.001	

Some trends can be discerned in the relative nucleophilicities.

Nucleophilicity *increases* as you go down a column in the periodic table. So I⁻ > Cl⁻, and -SH > -OH. This trend, which *opposes* basicity, is due to decreased solvation of lone pairs as the atoms bearing them become larger. The less solvated the lone pair, the more reactive it is toward an electrophilic C atom.

• Nucleophilicity parallels basicity when comparing nucleophiles in the same row of the periodic table. So $H_2N^- > HO^- > F^-$. Also, the order of nucleophilicity $MeO^- > HO^- > AcO^- > H_2O$ reflects the order of acidities of the conjugate acids, $MeOH < H_2O < AcOH < H_3O^+$.

• Nucleophilicity *decreases dramatically* as the nucleophile becomes bulkier. This is because the C atom in CH_3 -Br is attached to four groups, three of which are pointing towards the nucleophile as it approaches, whereas the H atom is attached only to one group. By contrast, basicity *increases slightly* with increased bulk. The order of basicities $HO^- < MeO^- < t$ -BuO⁻ is different from the order of nucleophilicities $HO^- < MeO^- < t$ -BuO⁻ is different from the order of MeO⁻, so their relative basicity determines their relative nucleophilicity.)

• Nucleophilicity increases dramatically in *polar aprotic* solvents (DMSO, DMF, HMPA) relative to *protic* solvents (H_2O , ROH). For example, F^- is a poor nucleophile and a poor base in protic solvents, but in polar aprotic solvents that have no acidic protons to bind tightly to the F^- , it is an excellent nucleophile and a pretty good base. Protic solvents have relatively acidic protons available for hydrogen bonding, whereas polar aprotic solvents don't.

Typical good nucleophiles/ poor bases: 2nd row or heavier atoms such as I⁻, Br⁻, RS⁻, and R₂S. Typical good nucleophiles/ good bases: first row elements with small groups attached, such as HO⁻, RO⁻, H₂N⁻, and H₃N. Typical good bases/ poor nucleophiles: first row elements with large groups attached, such as *t*-BuOK, *i*-Pr₂NLi (lithium diisopropylamide, LDA), *i*-Pr₂NEt.

Consistent with these guidelines, all C σ bond or lone pair nucleophiles are good bases. The two types of C nucleophiles that are sp-hybridized, $\neg C \equiv N$ (cyanide) and RC $\equiv C^-$ (a deprotonated alkyne), are good nucleophiles. Because of increased steric hindrance, compounds with C(sp²)– and C(sp³)–metal bonds such as PhMgBr and CH₃Li are *poor nucleophiles*.

The substitution pattern at the electrophile also affects the choice of elimination vs. substitution. The $S_N 2$ mechanism has a very crowded transition state, with a pentavalent C atom. One can imagine that the energy of this crowded transition state would be very sensitive to steric bulk. On the other hand, E2 elimination requires only that the base make a new bond to a H atom, so it doesn't need to get too close to the electrophilic center.

• 1° Alkyl centers undergo $S_N 2$ substitution with good nucleophiles, whether they are good or poor bases. With good bases/ poor nucleophiles, E2 elimination occurs.

• 3° Alkyl centers are so hindered that they *never* undergo S_N^2 substitution. E2 elimination or no reaction occurs with these substrates.

• By contrast, 2° alkyl centers tend to undergo predominant $S_N 2$ substitution only with good nucleophiles *that are also poor bases*. E2 elimination predominates with good bases, but mixtures of substitution and elimination products are often obtained when the nucleophile is both a good nucleophile and a good base.

Nature of Electrophile	Poor Base/ Good nucleophile (P. S. or heavier)	Good Base/ Good nucleophile (1st row, unhindered)	Good Base/ Poor nucleophile (1st row, hindered)	
CH ₃ –X or PhCH ₂ X	$\frac{(1, 3, 3)}{S_N^2}$	S _N 2	$\frac{(10010 \text{ m}, \text{m}, $	
1° C(sp ³)–X	S _N 2	S _N 2	E2	
2° C(sp ³)–X	S _N 2	$E2 > S_N^2$	E2	
3° C(sp ³)–X	N.R.	E2	E2	

Here is a chart to help you remember. N.R.= no reaction.

When the substrate is 2° and the nucleophile is both a good nucleophile and a good base, subtle changes in substrates or reaction conditions can tilt the ratio of products dramatically from substitution to elimination, or vice versa. Cycloalkyl halides (halogen directly attached to ring atom) are especially prone to undergo E2 elimination instead of $S_N 2$ substitution, but 2° allylic halides C=C-C-X and 2° benzylic halides Ph-C-X are especially prone to undergo $S_N 2$ substitution instead of E2 elimination. The balance can be tilted toward substitution by carrying the reaction out in a polar aprotic solvent such as DMSO or DMF or by reducing the basicity of the nucleophile. For example, $-CH_2CO_2Et$ will undergo elimination with *i*-PrI, but $-CH(CO_2Et)_2$ will undergo predominantly substitution.

Reminder: Alcohols and alkyl fluorides are *not* good electrophiles under basic conditions! They never undergo substitution under basic conditions, and they undergo elimination only under *very* harsh conditions.

Note that we haven't said much about the effect of leaving group on the reaction pathway. Both S_N^2 and E2 mechanisms require a leaving group. The nature of the leaving group (good or bad) affects *whether* a reaction occurs, but its effect on *which* reaction occurs is minimal.

7.7. Substitution and Elimination under Acidic Conditions.

7.7.1. The S_N1 Mechanism for Substitution.

In the $S_N 1$ mechanism for substitution, the leaving group leaves first to generate an electron-deficient intermediate called a *carbocation*. This intermediate then combines with a nucleophile to give the product. This mechanism for substitution is called $S_N I$.



The S_N1 mechanism is commonly called a two-step mechanism, but it is important to realize that usually additional steps are required. For example, protonation of the leaving group (or reaction of the leaving group with some other Lewis acid) often occurs in a fast, reversible step before the leaving group leaves.



On the other hand, if the nucleophile is water, an alcohol, or a carboxylic acid, then deprotonation of O after the nucleophile adds to C constitutes a third, fast step. The deprotonation is required to give a neutral product.

$$\begin{array}{c} & & \\ & & & \\ & & & \\ & & \\ & & & \\ & & \\ & & & \\$$

A carbocation is electron-deficient, so it is by definition a Lewis acid. Lewis acids can be generated only under acidic conditions. Therefore, the $S_N l$ substitution mechanism can occur only under acidic conditions.

We can draw a reaction coordinate diagram for the S_N1 reaction. The carbocation is electron-deficient, so it is much higher in energy than either the starting materials or the product. The reaction coordinate diagram for the S_N1 mechanism then looks like a double-humped camel. There is a TS on the way from the starting material to the carbocation, and there is another TS on the way from the carbocation to the product.

The rate-limiting step in this reaction (the highest barrier the reactants have to surmount) is the formation of the high-energy, electron-deficient carbocation intermediate. Only one molecule is involved in formation of the carbocation, so the rate of the reaction is described by the following equation.

rate = k [alkyl halide]

In other words, the rate of the reaction is proportional *only to the concentration of the organic substrate*. We call this mechanism $S_N I$, for substitution–nucleophilic–unimolecular.

The dependence of the rate of a nucleophilic substitution reaction on the concentration of the nucleophile represents one way to determine whether a nucleophilic substitution is proceeding by the $S_N 1$ or $S_N 2$ mechanisms.

Some typical $S_N 1$ substitution reactions:

 $\begin{array}{l} H_2O + PhCMe_2Br \rightarrow PhCMe_2OH + HBr\\ EtOH + 2-hydroxytetrahydrofuran, cat. acid \rightarrow 2-ethoxytetrahydrofuran + H_2O\\ HCl + Me_3COH \rightarrow Me_3CCl + H_2O\\ MeCO_2H + CH_3CH_2CHICH_3 \rightarrow CH_3CH_2CH(OAc)CH_3 + HI \end{array}$

Note that nucleophiles are neutral in all cases. Also note that all entries are under acidic conditions or generate acidic by-products. Also note that the electrophile C in every example has at most one H attached; that is, the alkyl group in the electrophile is either 2° or 3°, but never 1° or Me. To explain the last fact, we need to learn about carbocations.

Students often ask why the leaving group leaves spontaneously. Ambient temperature provides a certain amount of thermal energy to molecules. The energy is distributed unevenly among the molecules in a sample (Boltzmann distribution) — some have more than the average amount of energy, and some less. If a compound can form a carbocation that is not too high in energy, and some of the molecules in a

sample have sufficient thermal energy to reach the TS leading to that cation, then poof! the leaving group can leave.

7.7.2. Carbocations.

The S_N1 mechanism for substitution involves a carbocation intermediate. Before we talk about how different compounds undergo substitution reactions at different rates, we need to discuss factors that affect the stability of carbocations.

Let's look at the electronic structure of a carbocation, for example the *t*-Bu cation. The central C atom is electron-deficient. It only has six electrons around it. It forms three σ bonds and no π bonds, so it has sp² hybridization. The unhybridized p orbital is empty and is perpendicular to the plane containing the groups attached to C. The electronic structure of carbocations is the same as that of BX₃ compounds!



Carbocations have an electron-deficient C atom with an empty p orbital. Any filled orbitals that overlap with the empty p orbital will provide some extra electron density to the electron-deficient C atom and thereby stabilize the carbocation. There are three ways that this can happen.

(1) Lone pair-bearing heteroatoms, usually O or N, directly attached to the electron-deficient C atom can stabilize the carbocation by sharing their lone pair (resonance). We have already discussed this in detail. O and N atoms are so good at stabilizing carbocations that the π bond description is the *dominant* resonance structure.



(2) Adjacent π bonds can stabilize a carbocation by resonance. If C1 is the electron-deficient atom, the π bond must be between C2 and C3 for stabilization to occur. The electron deficiency is then delocalized over C1 and C3. An *allylic cation* is a carbocation with an alkenyl group attached. A *benzylic cation* is a cation with a phenyl group attached.



(3) Adjacent C–C and C–H bonds (bonds to atoms bonded to the electron-deficient C atom) can stabilize the carbocation by sharing their electron density with it. This is called *hyperconjugation*. The more highly substituted a carbocation, the more adjacent C–H and C–C bonds there are, the more electron density can be shared with the electron-deficient C atom, and the more stable the carbocation is. The order of stability of simple carbocations is Me < 1° < 2° < 3°. It is very important to know this order of stability. *The CH*₃+ *and* 1° *carbocations are so high in energy that they should never be proposed as intermediates. Primary alkyl halides and alcohols never undergo the* S_N1 *substitution reaction*.



The order of importance of the three kinds of carbocation stabilization is: lone pair resonance > π bond resonance > hyperconjugation. All three kinds of stabilization involve the overlap of a filled orbital (non-bonding lone pair, π , or σ) with the empty C(p) orbital.

One more point about the stability of carbocations. Trisubstituted carbocations, i.e. carbocations derived from $C(sp^3)$ –X, are much more stable than di- and monosubstituted carbocations, i.e. carbocations derived from $C(sp^2)$ –X and C(sp)–X. The major reason is because di- and monosubstituted carbocations have fewer allylic bonds which can participate in hyperconjugation. Phenyl cations, $C_6H_5^+$, are particularly unstable. Mechanisms which involve di- or mono-substituted carbocations should be viewed with extreme suspicion, though they do occur very rarely.

Note: Grossman's Rule (draw in all the H atoms and C–H bonds near the reactive centers) is *very* important in drawing reactions of carbocations, because you have trivalent and tetravalent C atoms flying around. You *will* lose track of the H atoms if you don't follow Grossman's Rule! Please believe me!

7.7.3. Stereochemistry of the S_N1 Mechanism.

Consider an electrophile in which the electrophilic C atom is stereogenic. If it undergoes an $S_N 1$ substitution reaction, when the leaving group leaves, the electrophilic center becomes sp^2 -hybridized, losing its stereogenicity. When the nucleophile comes in, it should have no preference for adding to either face of the carbocation. We can therefore safely predict that *when a substrate undergoes nucleophilic substitution by the* $S_N 1$ *mechanism at a stereocenter that is configurationally pure, the stereocenter in the product is configurationally scrambled*. This phenomenon represents one way to determine whether a particular nucleophilic substitution is proceeding by the $S_N 1$ or the $S_N 2$ mechanism. We indicate a scrambled configuration with a squiggly bond.



If there are stereocenters in the electrophile in addition to the electrophilic C, then the other stereocenters can influence which face of the carbocation the nucleophile will attack. In that case, retention, inversion, or racemization may be observed. For example, in the carbohydrate-forming reaction shown below, the other stereocenters in the electrophilic alcohol cause the electrophilic C atom to *retain* its configuration upon S_N1 substitution.



7.7.4. Ethers from two alcohols.

Alcohols can be electrophiles under acidic conditions. Alcohols can also be nucleophiles under acidic conditions. Hence, an alcohol can react with an alcohol under acidic conditions to give an ether. In this case, how does one know which alcohol is the electrophile and which is the nucleophile? Simple: the alcohol that can make the lower-energy carbocation is the electrophile. In the example, the 3° alcohol is the electrophile, the 1° alcohol is the nucleophile, and the bridging O in the product derives from the nucleophile.



The reaction of two alcohols to form an ether is a key reaction of carbohydrates. Simple carbohydrates (monosaccharides) can act as electrophiles toward other carbohydrates to form polysaccharides, and they can act as electrophiles toward alcohols on the side chains of proteins (serine and threonine) to form glycoproteins. In vivo, an enzyme provides the necessary H⁺ and steers the reaction toward the desired product.



The reverse reaction, in which an ether acts as an electrophile, water is the nucleophile, and the products are two alcohols, also occurs by an S_N1 reaction.



7.7.5. The S_N2 Mechanism under Acidic Conditions.

The S_N1 mechanism for substitution cannot happen under basic conditions, because the S_N1 mechanism has a carbocation intermediate, and a carbocation is a strong Lewis acid, and one can't spontaneously generate a strong acid under basic conditions. Can the S_N2 mechanism happen under acidic conditions? Yes, under specific circumstances. First, the nucleophile must be a poor base such as Cl^- , Br^- , or I^- , and it must be present in high concentration. Second, the electrophile must be primary so that it cannot go ahead and form a carbocation under the acidic conditions. Third, the electrophile is almost always a primary alcohol, because alkyl halides are more conveniently allowed to react under basic conditions, whereas alcohols are only electrophiles under acidic conditions. Fourth, the conditions are usually harshly acidic. Under these circumstances, substitution occurs under acidic conditions by the S_N2 mechanism.

7.7.6. The E1 Mechanism for Elimination.

OR

In the E1 mechanism, the leaving group leaves *first* to generate a carbocationic intermediate. This intermediate then undergoes a *fragmentation* (one of the three fundamental reactions of carbocations) to give an alkene and H⁺. Sometimes a base such as the departed leaving group is shown providing a new bond to H⁺ at the same time that the C–H bond fragments, but sometimes no base is shown.



The transition state in this reaction occurs on the way to forming the high-energy carbocationic intermediate. Only one molecule is involved in the rds, the formation of the carbocation (hence the "1" in "E1"), so the rate of the reaction is described by the following equation.

rate = k [alkyl halide]

In other words, the rate of the reaction is proportional only to the concentration of the organic substrate.

Because the E1 substitution mechanism has a carbocationic intermediate, it can occur only under acidic conditions, and only 2° and 3° alkyl halides and alcohols can undergo E1 elimination. Examples of E1 eliminations:

7.7.7. Stereochemistry of the E1 Mechanism.

The stereochemical outcome of the E1 mechanism can be contrasted with that of the E2 mechanism. In the E1 mechanism, the configurational sense at the electrophilic C atom is lost completely upon formation of the carbocation. The two diastereomeric starting materials, in other words, converge to a single carbocationic intermediate, which may lose H⁺ from either of two conformational diastereomers to give the (*E*) and (*Z*) products in a particular ratio *that is independent of the configuration of the starting material*. Elimination that occurs by the E1 mechanism is *nonstereospecific*. (The ratio of products depends on the relative energies of the two conformational diastereomers of the carbocationic intermediate.)



7.7.8. Skeletal Rearrangements under Acidic Conditions.

We have seen that under acidic conditions, alkyl halides and alcohols can ionize to give carbocations. The carbocations can undergo addition of a nucleophile to give a substitution product (overall S_N1), or they can undergo fragmentation of an adjacent C–H bond to give an elimination product (overall E1). There is a third pathway that they can take. This pathway generates a new carbocation. It is called *rearrangement*, and it occurs via *1,2-shifts* of alkyl or H groups.

Consider the reaction of 3-methyl-2-butanol with HCl. Under these acidic conditions and in the presence of the good nucleophile Cl⁻ we expect to see 2-chloro-3-methylbutane as the product by S_N1 substitution. In fact, though, both 2-chloro-3-methylbutane and 2-chloro-2-methylbutane are obtained in about equal amounts! This result requires an explanation.



The expected product is easy enough to explain. The first two steps in this reaction are protonation of the O to give a better leaving group and departure of the leaving group H_2O to give a 2° carbocation at C2. C2 can then combine with Cl⁻ to give the expected product.



How do we explain the unexpected product? Let's work backwards. The product has a C–Cl bond. We know how to make those by combination of Cl^- with a carbocation. That means that we have to have an intermediate with a C3 carbocation. Somehow we have to get from the C2 carbocation, which we know how to make, to a C3 carbocation.



What happens? A *hydride* (H⁻, i.e. the H nucleus along with the two electrons in the C–H bond) can *shift* from C3 to C2 to give the 3° carbocation. This *1,2-hydride shift* is an example of a carbocation *rearrangement reaction*, one of the three fundamental reactions of carbocations. (The others are combination with a nucleophile, as in S_N1 , and fragmentation to give an alkene, as in E1.)



The ratio of the expected product to the unexpected product is determined by the rate of Cl⁻ addition to the C2 carbocation versus the rate of the fragmentation–reprotonation or the 1,2-hydride shift sequence.

Alkyl groups can also undergo 1,2-shifts. For example, reaction of AcOH with 3,3-dimethyl-2bromobutane provides a mixture of two products, one expected and one unexpected. The unexpected product can be explained by invoking a *1,2-methyl shift* of the C2 carbocation to give a C3 carbocation. The electrons in the C3–Me bond move away from C3 and to C2 to form a new C2–Me bond.



When do 1,2-shifts occur? They usually occur when rearrangement gives a new carbocation lower in energy. Because 3° carbocations are already quite low in energy, they rarely rearrange. Because 1° carbocations are so difficult to form in the first place, they never get the chance to rearrange. The 2° carbocations are low enough in energy to form in the first place, but they are high enough in energy that they can rearrange to make 3° carbocations. *Thus*, 2° *carbocations are most likely to rearrange*.

7.7.9. Predicting Substitution vs. Elimination under Acidic Conditions.

Acidic conditions are identified by the presence of Brønsted or Lewis acids. Under acidic conditions, alcohols (sometimes ethers) are used as substrates for substitution and elimination more often than haloalkanes. Under these conditions, the lousy leaving group HO⁻ (or RO⁻) is transformed into a good leaving group H₂O (or ROH) by reaction with H⁺.

Both the E1 and S_N 1 mechanisms require that a carbocation be formed at the electrophilic C. Whether substitution or elimination occurs under acidic conditions depends on the substitution at the electrophilic C and on the concentration of the nucleophile.

• Both 2° and 3° alcohols and alkyl halides can form reasonably stable carbocations. (The 2° carbocations derived from 2° alkyl halides or alcohols can undergo all the usual rearrangement reactions.) Once the carbocations are formed, either E1 or S_N1 can occur. S_N1 substitution tends to occur when there is a very high concentration of nucleophile. The S_N1 substitution will occur when:

1. the solvent is protic and nucleophilic, i.e., H_2O , ROH, or RCO_2H (the last also provides the acidic conditions);



2. the solvent is saturated with a good, nonbasic nucleophile like Cl⁻;



3. a nucleophile is in the same molecule as the electrophile and a five- or six-membered ring can form.



If no nucleophile is present in high local concentration, then fragmentation of the carbocation occurs to give the E1 elimination product.



• For 1° alcohols and alkyl halides, the carbocation required for either the S_N1 or the E1 mechanism is not sufficiently low in energy to be formed, so neither S_N1 nor E1 will proceed. The S_N2 mechanism requires a good nucleophile, one that is also a poor base (these are acidic conditions, after all); this condition is met only by heavy nucleophiles such as Br⁻, I⁻, or occasionally Cl⁻. Even with these nucleophiles, S_N2 substitution at 1° alcohols requires very harsh conditions, e.g. boiling in 48% aq. HBr. Under less harsh conditions, 1° alcohols and alkyl halides are simply not electrophiles under acidic conditions. (However, 1° alcohols can be *nucleophiles* toward 2° and 3° alkyl halides and alcohols under acidic conditions!)



7.28



In summary:

Nature of Electrophile	Low concentration of	High concentration of	
(X=OH, OR, or halogen)	nucleophile	nucleophile	
1° C(sp ³)–X	no reaction	S_N^2 with conc. HX	
2° C(sp ³)–X	E1 (maybe rearrangement)	$S_N 1$ (maybe rearrangement)	
3° C(sp ³)–X	E1	S _N 1	

Remember: The nucleophiles in S_N1 reactions must be poor bases, because strong bases cannot exist under the acidic conditions required for the S_N1 reaction. The nucleophiles in S_N1 reactions are most commonly lone pair nucleophiles such as alcohols, halides, and carboxylic acids.

7.8. Using Substitution Reactions in Synthesis.

A common question in organic chemistry is, "How would you make this compound from simpler starting materials?" To solve such a problem, you need to be able to work both backwards and forwards. You also need to be able to see the forest for the trees. Organic chemistry requires you to work at several different levels. At one level, we say, "This alcohol group can be converted into this bromide," or, "This alkene can be made from this alkyl halide." Consider this level as the forest. At a more detailed level, we say, "We can use these reagents to convert an alcohol into an alkyl bromide," or, "This elimination reaction requires a good base." Consider this level as the trees. At an even more detailed level, we say, "Here is the S_N1 mechanism by which this substitution reaction occurs," or "This elimination reaction occurs by the E2 mechanism." Consider this level as the leaves. It is essential that you not lose the forest for the trees, the trees for the leaves, the forest for the leaves, or vice versa!

Synthesis problems require you to work at the levels of the forest and the trees. Start off at the forest, work your way down to the trees, and if the trees don't make sense, go back up to the level of the forest.

7.8.1. Retrosynthetic analysis.

Because we have just spent so much time learning about substitution reactions, we can guess that we will use substitution reactions to make our target compounds from simpler starting materials. The skill

of figuring out what starting materials can be used to make a desired product is called *retrosynthetic analysis*. We use a double-bodied arrow, \Rightarrow , to show a retrosynthetic step leading from product to starting materials. The arrow should be read, "can be made from".

To identify the simpler starting materials, we need to identify the bond that can be formed by a substitution reaction. In other words, if we cleave that bond, protonate one of the atoms to make it neutral, and attach a leaving group to the other one, we should have two starting materials that will react to give the desired product. The process of breaking a bond to give two simpler starting materials is called a *disconnection*.

What makes a good disconnection?

• A bond between a heteroatom and $C(sp^3)$. Most of the nucleophiles we have learned about have been heteroatoms. Add a proton to the heteroatom after you do the disconnection (unless it is positively charged before the disconnection), and attach a leaving group (typically Br or OTs) to $C(sp^3)$.



• A bond between C(sp) and C(sp³). The C(sp) carbanion is a good nucleophile because it is fairly unhindered. Alkynes RC=CH are easy to deprotonate, and -C=N is a common and inexpensive anion. Add a proton to C(sp) after you do the disconnection, and attach a leaving group (typically Br or OTs) to C(sp³). The substitution reaction of -CN or $RC=C^-$ with an alkyl halide is an important method of preparing C-C bonds, the essence of organic synthesis!



In most cases, Br is a good leaving group. One can just as well use Cl, I, or OTs as the leaving group, but alkyl bromides are easy to make and are good electrophiles. However, because it is exceedingly difficult to make or obtain alkyl bromides in configurationally pure form, do not use Br as the leaving group if your electrophilic atom is a configurationally pure stereocenter. Instead, use OTs or OMs as the leaving group, and invert the configuration of the electrophilic center in the starting material. The tosylate will itself be made from the corresponding alcohol with the *same* configuration as the tosylate.



If the alkyl bromide is not a permissible starting material (you will know whether it is from the instructions you are given), you can make it from the corresponding alcohol.



7.8.2. Working forward.

After you have disconnected a bond and drawn your two starting materials, you need to decide whether you should make the bond under basic conditions or acidic conditions. Look at your electrophile. If your electrophile is a 1° halide, the conditions will have to be basic because 1° halides don't do substitution under acidic conditions (most of the time). If your electrophile is a 3° halide, the conditions will have to be acidic because 3° halides don't do substitution under basic conditions. The 2° halides can undergo substitution under acidic or basic conditions, but basic conditions are preferred so that rearrangements don't occur.

You may want to look at your nucleophile, too. For example, if the nucleophilic atom is C, it doesn't have a lone pair in its protonated state, so obviously you will need to deprotonate it before it can react with an electrophile, so your conditions will have to be basic. Heteroatom nucleophiles, on the other hand, have lone pairs even when they are in their neutral, protonated form.

After you have determined whether the conditions are acidic or basic, you need to determine whether the reaction will work as written. For example, in the first disconnection below, the alkyl halide is 1°, so the conditions have to be basic if a substitution is going to occur. However, deprotonation of the alcohol gives a species that is a poor nucleophile/good base because it is very sterically hindered, so the desired substitution reaction will not proceed. If your disconnection gives two starting materials that won't do a substitution reaction under either acidic or basic conditions, you need to look for another disconnection. In the case below, the second disconnection gives an alcohol and a 3° alkyl halide that will give the substitution product nicely under acidic conditions.



If the conditions are basic, what base should be used? The base must be strong enough to remove the proton from the nucleophile, and it must be nonnucleophilic so it doesn't react with the electrophile. Alkynes are often deprotonated with BuLi or NaNH₂. Alcohols are often deprotonated with NaH or Na metal because the by-product, H_2 , bubbles away as a gas. Amines are usually not deprotonated at all, because they already have a reactive lone pair.



C atoms adjacent to a single carbonyl or CN group are often deprotonated with LDA, whereas C atoms flanked by two carbonyl or CN groups are often deprotonated with NaOEt. These reactions will be much more important later in this course.



If the protonated nucleophile is a good acid with $pK_a < 12$ (HCN, HCl, HOAc), instead of using the protonated nucleophile, it's better just to use a metal salt of the nucleophile (NaCN, KCl, LiOAc).

If the conditions are acidic, and the nucleophile is a good acid or the electrophile is an alkyl halide, there is no need to add an acid to the reaction. If the nucleophile is an alcohol or water and the electrophile is an alcohol or ester, a catalytic amount of a very strong acid such as TsOH can be added.

If you need to convert an alcohol to an alkyl bromide, use PBr_3 , regardless of whether the alcohol is 1°, 2°, or 3°. The mechanism of the reaction of an alcohol with PBr_3 proceeds in two steps. In the first step, the O of the alcohol does an S_N2 -type substitution on P to replace a P–Br bond with a P–O bond. In the second step, the C–O bond is replaced with a C–Br bond in either an S_N1 or an S_N2 substitution reaction, depending on whether the alcohol is 1°, 2°, or 3°.

7.9. Using Elimination Reactions in Synthesis.

For several reasons, the use of elimination reactions in synthesis is considerably less complicated than the use of substitution reactions. The elimination reaction doesn't involve the union of two separate starting materials to make products, and the elimination reaction always gives an alkene. Still, there are some subtleties to the use of elimination reactions in synthesis that bear discussion.

As always, if you are asked to make a target compound from some starting material, you must ask yourself, what starting material could I make this compound from? If your target compound is an alkene, you can always make the alkene from an alkyl halide. One of the C atoms of the alkene in the target will bear a leaving group, in the starting material, and the other will bear a H atom. Also, the starting material will lack the π bond. As before, Br makes a good leaving group. *Don't forget to obey Grossman's rule!*



If the target alkene is unsymmetrical, two different starting materials can be drawn. In that case, you need to choose which starting material is a better one. The better starting material is the one that will give you the largest proportion of the desired product by Zaitsev's rule. In the first case below, both starting materials can give only the desired product by an elimination reaction. In the second case below, Zaitsev's rule tells you that elimination of HBr from the first starting material would give predominantly the endocyclic alkene. As a result, the second starting material is a much better one.



Once you have chosen the starting material, you need to decide what reaction conditions to apply in the forward direction. If the starting material is a 3° alkyl halide, you can use acidic or basic conditions. If the starting material is a 2° alkyl halide, acidic conditions might give rearrangements, so basic conditions are preferred. If the starting material is a 1° alkyl halide, elimination cannot occur under acidic conditions, so basic conditions are preferred. In short, basic conditions work for any kind of alkyl halide. However, Zaitsev's rule is more rigorously enforced under acidic conditions than under basic conditions, so you do want to consider the possibility of an elimination under acidic conditions if your electrophile is 3°. Also, if the starting material is a 3° alkyl halide, you will likely have to make it from the 3° alcohol anyway, so it is usually better to replace the Br in the starting material with OH and carry out the elimination under acidic conditions.



Zaitsev gives only desired Zaitsev can give two products

instead of 3° bromide, eliminate 3° alcohol under acidic conditions:



If the conditions are basic, the last step is to choose an appropriate base. The best base is one that is also a poor nucleophile, especially for 1° alkyl halides that would rather undergo $S_N 2$ than E2. Common bases for elimination reactions include *t*-BuOK, EtN(*i*-Pr)₂, and a base called DBU that contains a particularly basic *amidine* substructure (N=C–N).