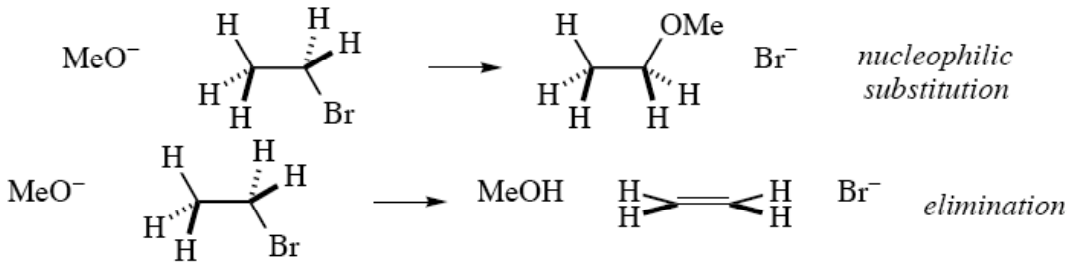
Substitution and Elimination Reactions.

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 arrangment 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 idea about how the reaction occurred is correct.

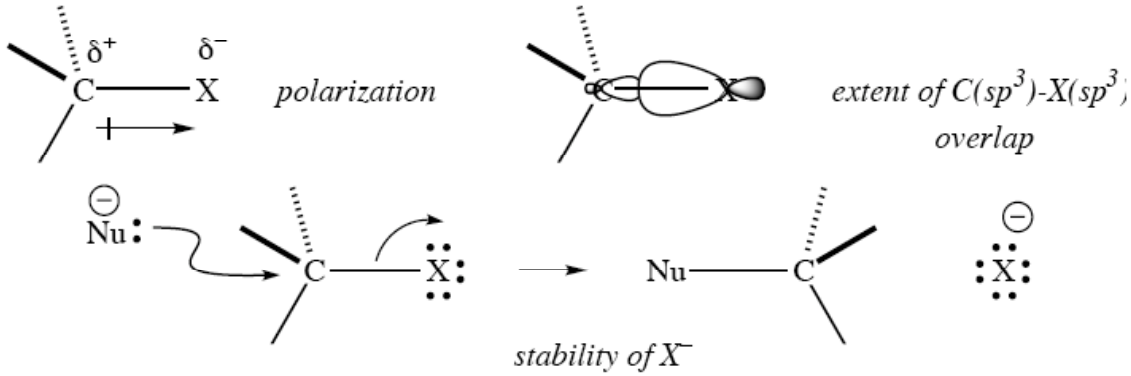
We will see soon that there are two mechanisms by which nucleophilic substitution can occur, and there are two mechanisms by which elimination can occur. The purpose of this chapter is to learn how the reaction conditions and the structures of the Lewis base and the substrate affect the relative rates 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. Leaving Groups.

All substitution and elimination reactions require a σ bond electrophile. The most common such electrophile is a haloalkane, RX, where the leaving group is halide, X^-. Different halides, though, 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.

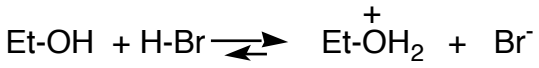
• The *polarization* of the C–X bond. The more polarized the bond, the better the leaving group. The bond polarization decreases with decreasing electronegativity of X, i.e. in the order F > Cl > Br >> I. The actual order of leaving group ability is I^- > Br^- > Cl^- >> F^-.

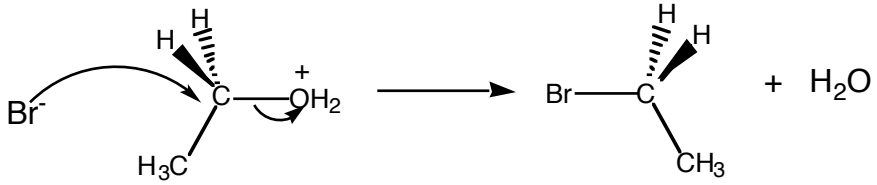


In fact, alkyl fluorides are nearly inert to substitution or elimination (hence the stability of Teflon). Other electronegative groups, e.g. RO^-, can also act as leaving groups in principle. Comparing F^- and HO^-, both are about the same size, but F^- is more electronegative. So we can conclude that 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 haven't discussed, or when extremely harsh conditions are used (i.e., 50% aq. KOH).

There are several ways to make HO^- is better leaving group:

(1) Protonate the alcohol with a strong acid to get the conjugate acid of the alcohol. E.g.



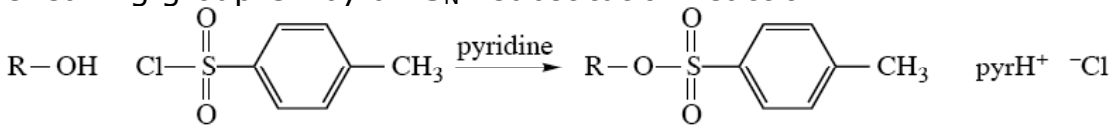


This converts a poor leaving group HO^- into the pretty good leaving group OH_2 (leaving group ability ≈ Cl^-). Alcohols ROH are weak bases, with p*K*a of their conjugate acids ROH_2^+ ≈ 0, so an alcohol ROH is only protonated under acidic conditions to give ROH_2^+, an electrophile with a pretty good leaving group. This does not happen under basic conditions. *Alcohols are electrophiles under acidic conditions, but not under basic conditions.*

(2) Replace the H in HO^- with more electronegative groups.

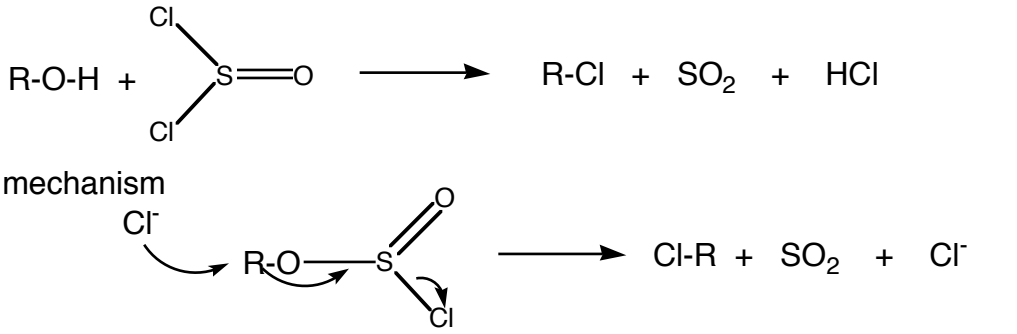
When H is replaced with $RS(O)_2$, one obtains a very important class of leaving groups, the sulfonate esters. The most common sulfonates, RSO_3^-, are tosylate (short for toluenesulfonate, $^-$OTs) and mesylate ($^-$OMs, short for methanesulfonate). Tosylates and mesylates are easily

made from alcohols and tosyl chloride TsCl or mesyl chloride MsCl. The O of the alcohol acts as a nucleophile toward electrophilic S, displacing the leaving group Cl^- by an S_N2 substitution reaction.

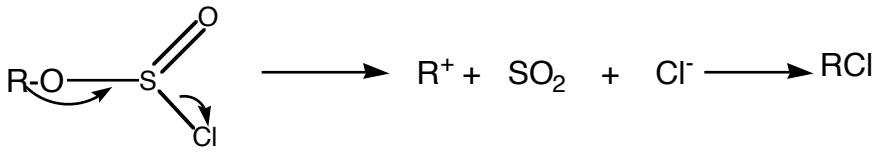


The conversion of an alcohol to a tosylate represents a way of turning a lousy leaving group, ^-OH, into a good leaving group, ^-OTs (leaving group ability ≈ Br^-). Tosylates are sometimes called *pseudohalides,* because their properties are similar to the halides. From now on, whenever we say halides,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

A variation on the sulfonate reaction involves treatment of alcohols with thionyl chloride $SOCl_2$ – this initially gives a chlorosulfite ester which can decompose by a SN2 pathway or direct decomposition to SO_2 and ion recombination



chlorosulfite ester



chlorosulfite ester

This reactions results in conversion of the HO^- poor leaving group into a good one (SO_2 and Cl^-).

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, $NaNH_2$, EtSK, $CH_3CH_2CH_2CH_2ONa$, NaBr) or a neutral compound with a lone pair (R_3N, H_2O, ROH, RCO_2H, R_2S, R_3P).

See **Jones, Table 7.3**

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. Substitutions are usually carried out under basic or acidic conditions.

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 or they are anionic but from the 3rd row of the periodic table or below (usually Cl^-, Br^-, or I^-). **Under basic conditions, though, any nucleophile can exist**.

7.4. Mechanisms of Substitution Reactions.

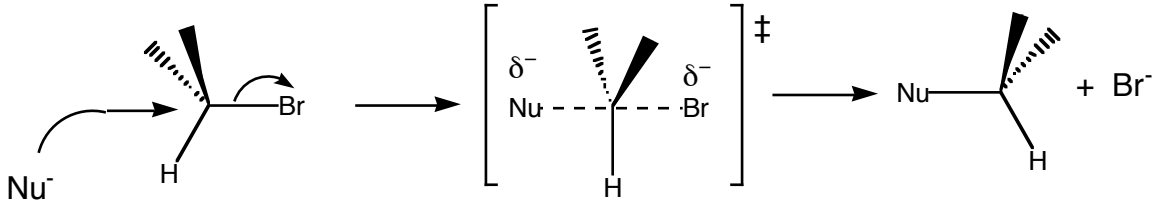
Let's look at the mechanism of nucleophilic substitution reactions. Substitution can in principle occur in three ways.

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 way requires a 10-electron C intermediate, though, so it doesn't occur at electrophilic tetrahedral C atoms. (It can occur in substitutions at transition metals and certain heavy atoms, however.)

7.4.1. S_N2 Mechanism.

In the first mechanism for substitution, 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.



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:

$$\text{rate} = k\,[Nu^-][\text{alkyl halide}]$$

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 ***SN2,*** for ***substitution/nucleophilic/bimolecular.***

Some typical S_N2 substitution reactions:

$HO^- + CH_3I \longrightarrow HOCH_3 + I^-$

$EtS^- + CH_3CHClCH_3 \longrightarrow H_3CH(SEt)CH_3 + Cl^-$

$Et_3N + PhCH_2Br \longrightarrow [Et_3N^+CH_2Ph]Br^-$

KOAc + bromocyclohexane $\longrightarrow$ cyclohexyl acetate + KBr

$BuNH_2 + CH_3CH_2CH(Br)CH_3 \longrightarrow [CH_3CH_2CH(N^+H_2Bu)CH_3]Br^-$

(after work-up, $CH_3CH_2CH(NHBu)CH_3$)

$HBr + PhCH_2CH_2OH \longrightarrow PhCH_2CH_2Br + H_2O$

Note that the electrophilic 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_N2 substitution reaction.

We can draw a reaction coordinate diagram for the S_N2 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_N2 substitution reaction has a particularly simple reaction coordinate diagram: starting materials, a single transition state, and products.

See **Jones, Figure 7.23**

In the S_N2 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_N2 substitution reactions!*

- See **Jones, Table 7.1**

Note also that nucleophiles can be neutral or anionic. Also note that most entries are under basic conditions. (The last entry shows that the S_N2 reaction can occur under acidic conditions under special circumstances which we will discuss soon; for now, note that the OH acts as a leaving group in this case only because the conditions are acidic.)

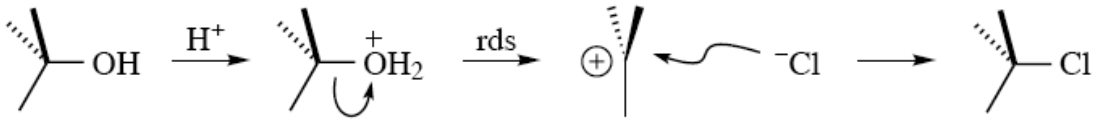
Some notes on conventions. I've written out the nonorganic products in all cases, but in fact we often omit the nonorganic products. The fifth entry shows that a nucleophile with an acidic H can lose that H after the substitution reaction to regenerate a neutral compound; we often omit the intermediate 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 nucleophile above the arrow and the solvent below the arrow.

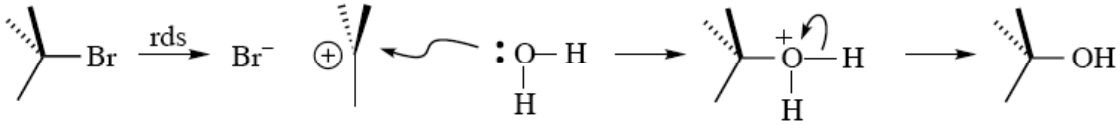
7.4.2. S_N1 Mechanism.

In the second possible mechanism for substitution, the leaving group might leave *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_N1*.

The SN1 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.



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_N1 substitution mechanism can occur only under acidic conditions**.

We can draw a reaction coordinate diagram for the SN1 reaction. The carbocation is electron deficient, so it is much higher in energy than either the starting materials or the product. – see **Jones, Fig 7.60**. 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.

$$\text{rate} = k\,[\text{alkyl halide}]$$

In other words, the rate of the reaction is proportional *only to the concentration of the organic substrate.* We call this mechanism ***S_N1,*** for ***substitution/nucleophilic/unimolecular.***

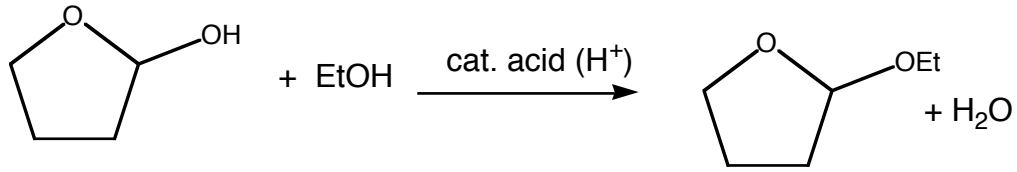
The dependence of the rate of a nucleophilic substitution reaction on the concentration of the nucleophile represents one way to determine whether a nucleophilic substitution is proceeding by the SN1 or SN2 mechanisms (S_N1 reactions are independent of nucleophile concentration)

Some typical S_N1 substitution reactions:

$$H_2O + PhCMe_2Br \longrightarrow PhCMe_2OH + HBr$$

$$HCl + HOCMe_3 \longrightarrow ClCMe_3 + H_2O$$

$$MeCO_2H + CH_3CH_2CHICH_3 \longrightarrow CH_3CH_2CH(OAc)CH_3 + HI$$

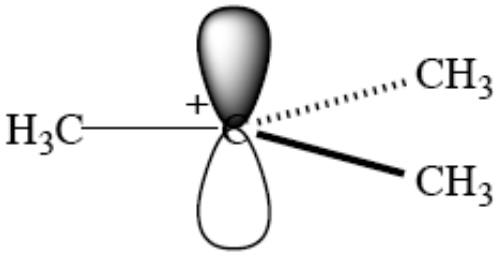


Note that nucleophiles are neutral in all cases. Also note that all entries are under acidic conditions or generate acidic by-products. Also note that the electrophile C in every example has <u>at most</u> one H attached; that is, the alkyl group in the electrophile is either 2° or 3°, but never 1° or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

7.4.3. Carbocations.

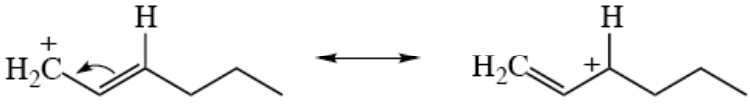
The S_N1 mechanism for substitution involves a carbocation intermediate. Before we talk about how different compounds undergo substitution reactions at different rates, we need to discuss factors that affect the stability of carbocations. Let's look at the electronic structure of a carbocation, for example 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 sp^2 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 BX_3 compounds!

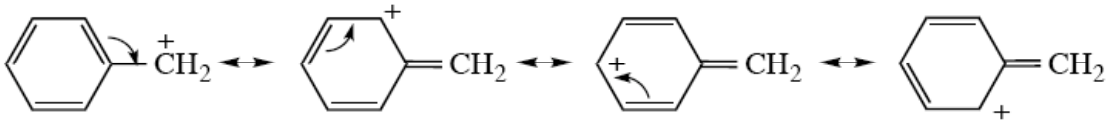
Carbocations have an electron-deficient C atom with an empty p orbital. Any filled orbitals that overlap with the empty p orbital will provide some extra electron density to the electron-deficient C atom and thereby stabilize the carbocation. There are three ways that this can happen.



(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.

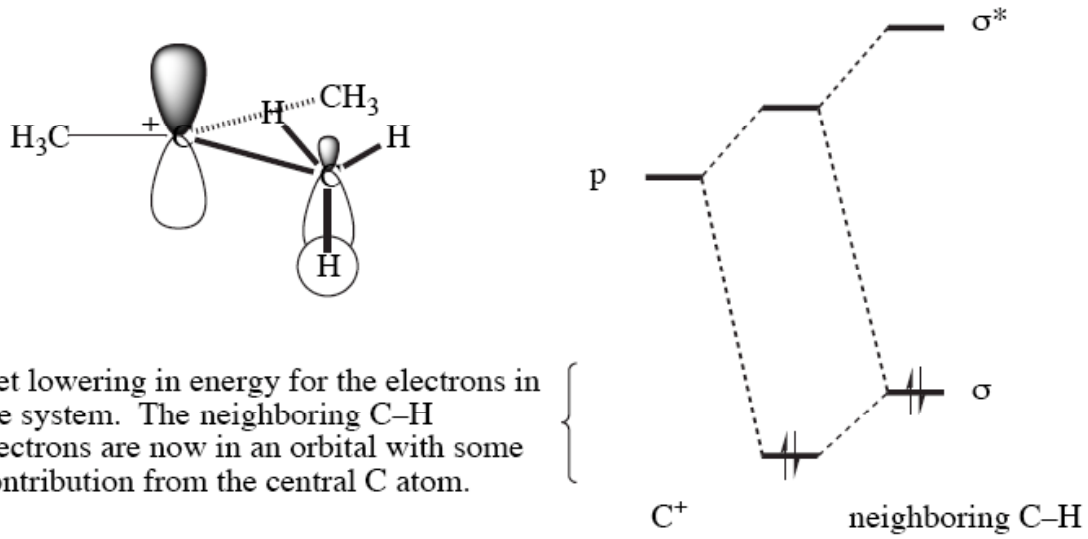
(2) Adjacent π bonds can stabilize a carbocation by resonance. If C1 is the electron-deficient atom, the π bond must be between C2 and C3 for stabilization to occur. The electron deficiency is then delocalized over C1 and C3. An *allylic cation* is a carbocation with an alkenyl group attached. A *benzylic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

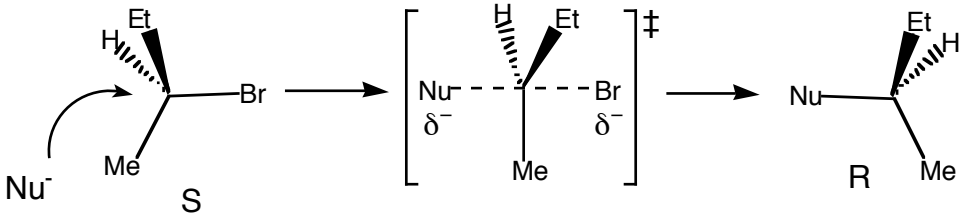
One more point about the stability of carbocations. Trisubstituted carbocations, i.e. carbocations derived from C(sp^3)–X, are much more stable than di- and monosubstituted carbocations, i.e. carbocations derived from C(sp^2)–X and C(sp)–X. The major reason is because di- and monosubstituted carbocations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

Note: drawing in all the H atoms and C–H bonds near the reactive center is *very* important in drawing reactions of carbocations, because you have trivalent and tetravalent C atoms flying around and it is easy to lose track of the H atoms.

7.4.4. Stereochemistry of the S_N2 and S_N1 Mechanisms.

Let's look at the stereochemistry of the SN2 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_N2 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



if Nu^- has same CIP priority as Br^-

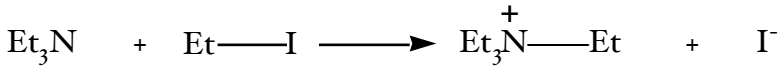
start off with (*S*)-2-bromobutane, and if the incoming nucleophile has the same CIP priority as the leaving group, then the product has the absolute (*R*) configuration. We call this the *Walden inversion.* (Don't confuse this inversion with the lone pair inversion that occurs so easily in amines.) 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.*

By contrast, in the S_N1 reaction, an achiral intermediate, the carbocation, is obtained. (see, **Jones, Fig 7.56**) Remember that optically inactive starting materials or intermediates always give optically inactive products. If the product in an S_N1 reaction is chiral, it must be racemic. We can therefore safely predict that *when a substrate undergoes nucleophilic substitution by the S_N1 mechanism at a stereocenter that is configurationally pure, the stereocenter in the product is configurationally scrambled.* This represents a second way to determine whether a particular nucleophilic substitution reaction is occuring by the S_N1 or the S_N2 mechanism.

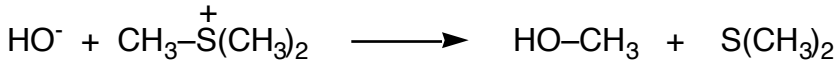
Kinetics and stereochemistry represent the two best ways to determine whether a particular reaction has proceeded by the S_N1 mechanism or the *S_N2* mechanism. Another way is to determine the dependence of the rate of the reaction on the polarity of the solvent.

The rate-determining step (rds) of the S_N1 reaction gives a carbocationic intermediate, whereas the rds of the S_N2 reaction does not. Polar solvents will stabilize the TS relative to starting materials in S_N1 reactions (by dipole–dipole interactions) much more than they will S_N2 reactions, so we can conclude that polar solvents will accelerate S_N1 reactions relative to non-polar solvents much more than they will S_N2 reactions.

Note in fact that as solvent polarity is increased, some S_N2 reactions go faster while some go slower.



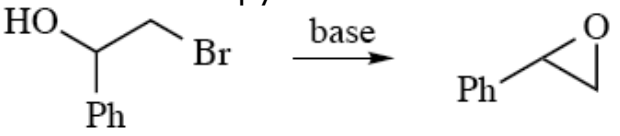
rate increases as solvent polarity increasea

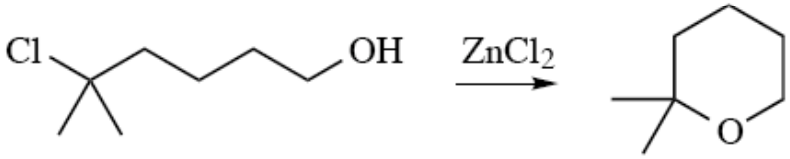


rate decreases as solvent polarity increasea

7.4.5. Intramolecular Substitutions.

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, S_N1 or S_N2, 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.





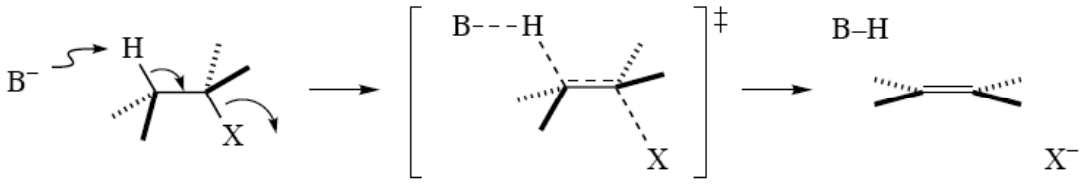
7.5. Mechanisms of Elimination Reactions.

Now let's look at the mechanism of elimination reactions. We have to

break two bonds: the C–H bond and the C–X bond. The H makes a new bond to a base. We can imagine three different ways in 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.

7.5.1. E2 Mechanism.

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_N2 mechanism, has no intermediates. The rate-determining step is bimolecular; that is, the rate of the reaction is described by the following equation.

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

(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, <u>any kind of alkyl halide (1°, 2°, 3°) can undergo E2 elimination, as long as there is a C–H bond adjacent to the leaving group</u>. CH_3X and $PhCH_2X$ electrophiles cannot undergo E2 elimination. Examples of E2 eliminations:

$$t\text{-BuO}^- + CH_3CH_2I \rightarrow CH_2{=}CH_2 + \text{t-BuOH} + I^-$$

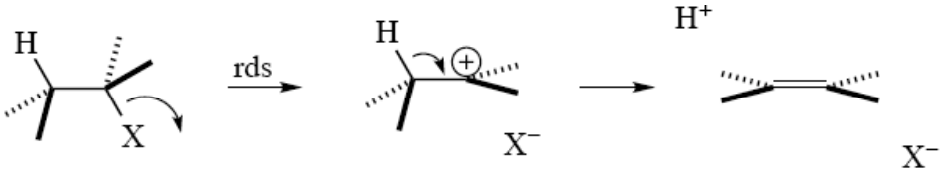
$$KOH + \text{bromocyclohexane} \rightarrow \text{cyclohexene} + KBr$$

$$Et_3N + PhCH_2CH_2OTs \rightarrow PhCH{=}CH_2 + Et_3\overset{+}{N}H\ TsO^-$$

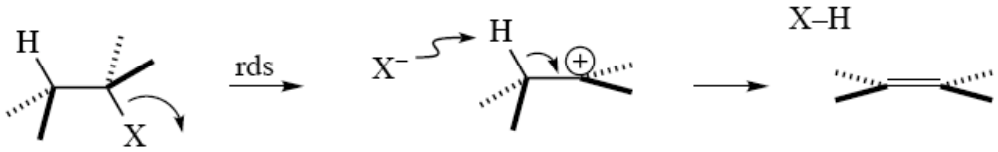
$$EtO^- + \text{1-methyl-1-chlorocyclopentane} \rightarrow \text{1-methylcyclopentene} + EtOH + Cl^-$$

7.5.2. E1 Mechanism.

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.



OR



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.

$$\text{rate} = k\,[\text{alkyl halide}]$$

In other words, the rate of the reaction is proportional *only to the concentration of the starting 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:

$$PhCMe_2OH + \text{cat. acid} \rightarrow Ph(Me)C{=}CH_2 + H_2O$$

$$PhC(OEt)_2CH_2CH_3 + \text{cat. acid} \rightarrow PhC(OEt){=}CHCH_3 + EtOH$$

$$RCO_2CMe_3 + \text{cat. } CF_3CO_2H \rightarrow RCO_2H + Me_2C{=}CH_2$$

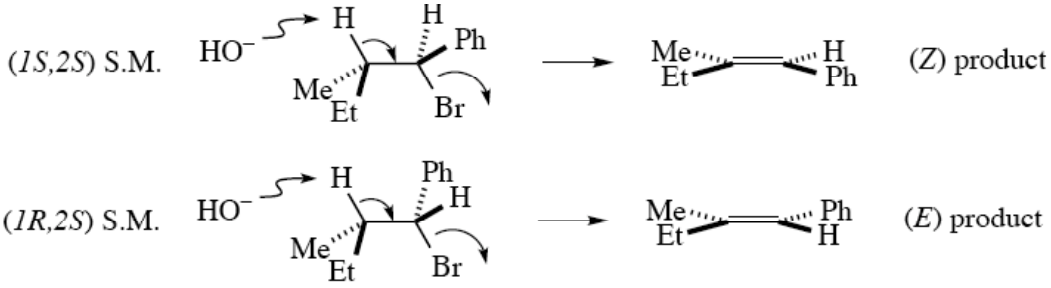
7.5.3. Zaitsev's Rule.

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 (due to reduced steric strain).

So the major product is expected to be *trans*-2-butene (this phenomenon is termed *Zaitsev elimination*).
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.
There is another type of elimination, called *Hofmann elimination*, in the major product is the less substituted alkene. Hofmann elimination applies only when the leaving group is a fluoride or onium ion (such as R_3N^+ or R_2S^+). We won't talk about this in any detail since the major product in most E1 or E2 eliminations is the most substituted alkene.

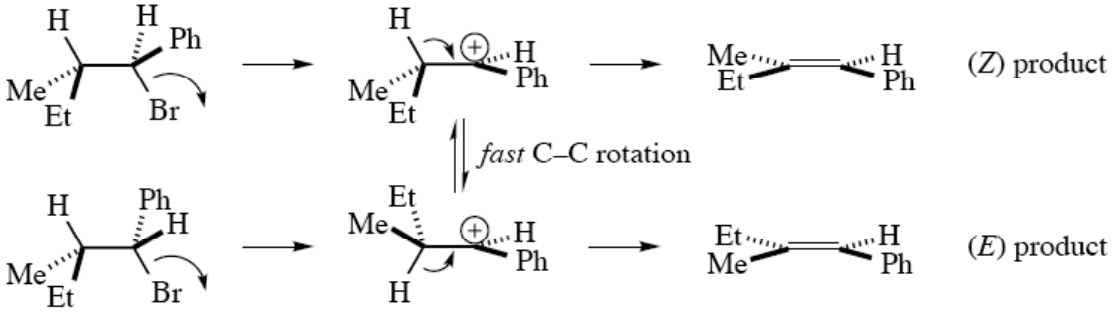
7.5.4. Stereochemistry of the E1 and E2 Mechanisms.

Sometimes Zaitsev's rule does not apply to E2 eliminations. This is true when there is only one H on the C adjacent to the electrophilic center that can be removed to give an alkene. *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 *anti-periplanar* 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.*

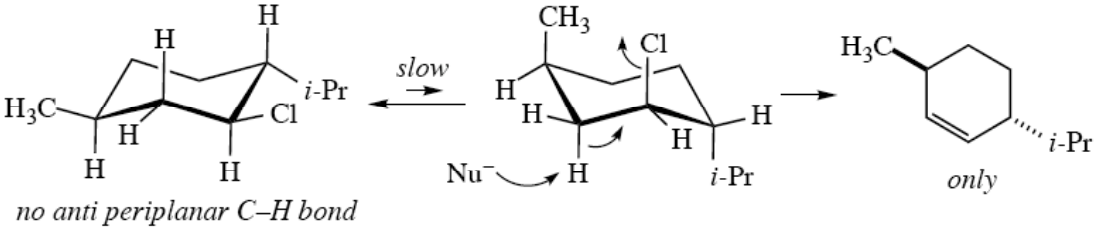


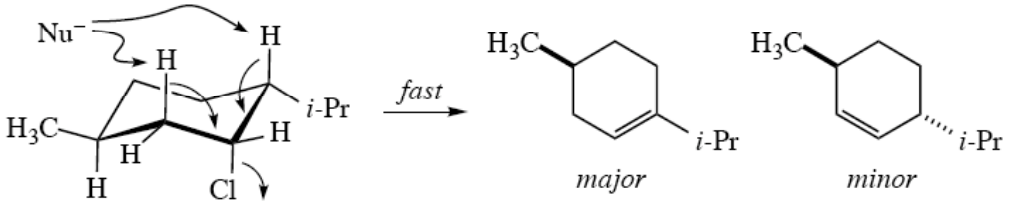
In acyclic compounds, the requirement for anti-periplanarity in E2 eliminations has consequences only when both the electrophilic C and the one adjacent to it are stereocenters.
The stereochemical outcome of the E1 mechanism can be contrasted with that of the E2 mechanism. In the E1 mechanism, the configurational 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.)



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 stablest 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 stablest conformer has the C–Cl bond axial. Two of the adjacent C–H bonds are axial, so elimination from neomenthyl chloride gives two products, with the more substituted (stabler) isomer predominating. Elimination from neomenthyl choride 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.
Kinetics and stereochemistry represent two ways to determine whether a particular elimination has proceeded by the E1 mechanism or the E2 mechanism. Another way is to determine the effect of solvent polarity on the rate of the reaction. Polar solvents will accelerate E1 reactions relative to non-polar solvents much more than they will E2 reactions, for reasons which we discussed earlier in the context of substitution reactions.

7.6. Predicting Substitution vs. Elimination.

In principle, any nucleophile is also a base, so in principle, any compound with a lone pair of electrons can react with an alkyl halide to give either substitution or elimination. When we carry out a reaction we want to be able to predict whether it will result in substitution or elimination. Empirical guidelines that allow us to predict (more or less) when substitution will occur and when elimination will occur have been developed from correlating the results of many experiments. These are only guidelines, and they sometimes fail, but they're the best we've got. The guidelines are very different under basic conditions and under acidic conditions. The guidelines require that you look at the hybridization and substitution of the electrophilic C and at the nature of the nucleophile.

7.6.1. 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_N1 substitutions and E1 eliminations can occur only under acidic conditions. Therefore, *under basic conditions, any substitution at C(sp^3) 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. CH_3Br. - **See Jones fig 7.32**

The different natures of H^+ (cationic, electron-deficient, very small, unhindered) and CH_3Br (neutral, electron-saturated, bigger, more hindered) mean that the reactions have slightly different preferences for the nature of the nucleophilic atom.

$$Nu^- + CH_3Br \longrightarrow CH_3Nu + Br^-$$

Nu:	^-SH	^-CN	I^-	MeO^-	HO^-	Cl^-	$:NH_3$	$H_2O:$
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 increasing squishiness (*polarizability*) of atoms as they become larger.

• 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 < $H3O^+$.

• 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^-. (There's not much difference in bulk between HO^- and 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 R_2S.

Typical good nucleophiles/good bases: first row elements with small groups attached, such as HO^-, RO^-, H_2N^-, and H_3N.

Typical good bases/poor nucleophiles: first row elements with large groups attached, such as *t*-BuOK, *i*-Pr_2NLi (lithium diisopropylamide, LDA), *i*-Pr_2NEt.

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, $^-C{\equiv}N$ (cyanide) and $RC{\equiv}C^-$ (a deprotonated alkyne), are good nucleophiles. Because of increased steric hindrance, compounds with $C(sp^2)$– and $C(sp^3)$–metal bonds such as PhMgBr and CH_3Li are *poor nucleophiles*.

The substitution pattern at the electrophile also affects the choice of elimination vs. substitution. The S_N2 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 does not need to get too close to the electrophilic center.

- 1° Alkyl centers undergo S_N2 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_N2 substitution. E2 elimination or no reaction occurs with these substrates.
- By contrast, 2° alkyl centers undergo S_N2 substitution only with good nucleophiles *that are also poor bases.* E2 elimination occurs with good bases, whether they are good or poor nucleophiles. Mixtures of products are often obtained with 2° alkyl halides. Cycloalkyl halides (halogen directly attached to ring atom) are especially prone to undergo E2 elimination instead of S_N2 substitution, but 2° allylic halides C=C–C–X and 2° benzylic halides Ph–C–X are especially prone to undergo S_N2 substitution instead of E2 elimination. The balance can be tilted toward substitution by carrying the reaction out in a polar aprotic solvent.

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

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 $PhCH_2X$	S_N2	S_N2	S_N2 or N.R.
1° C(sp^3)–X	S_N2	S_N2	E2
2° C(sp^3)–X	S_N2	E2 (some S_N2)	E2
3° C(sp^3)–X	N.R.	E2	E2

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_N2 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.

7.6.2. Acidic Conditions.

Acidic conditions are identified by the presence of Brønsted or Lewis acids. Under acidic conditions, alcohols (sometimes ethers) are used

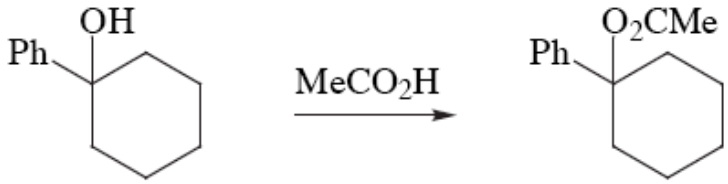
as substrates for substitution and elimination more often than haloalkanes. Under these conditions, the lousy leaving group HO^- (or RO^-) is transformed into a good leaving group H_2O (or ROH) by reaction with H^+.

Both the E1 and S_N1 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.

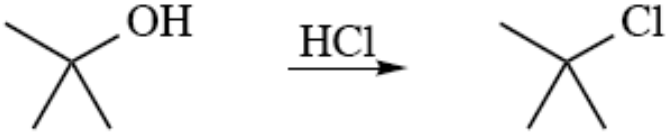
• Both 2° and 3° alcohols and alkyl halides can form reasonably stable carbocations. (The 2° carbocations derived from 2° alkyl halides or alcohols can undergo all the usual rearrangement reactions.) Once the carbocations are formed, either E1 or S_N1 can occur. S_N1 substitution tends to occur when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

when:

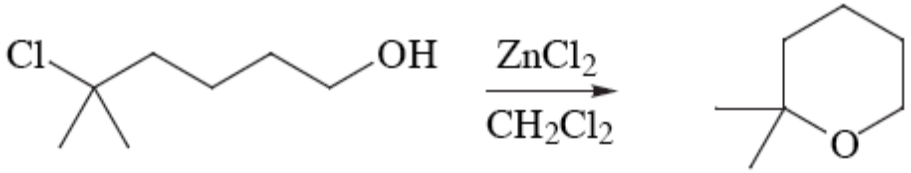
1. the solvent is protic and nucleophilic, i.e., H_2O, ROH, or RCO_2H (the last also provides the acidic conditions);



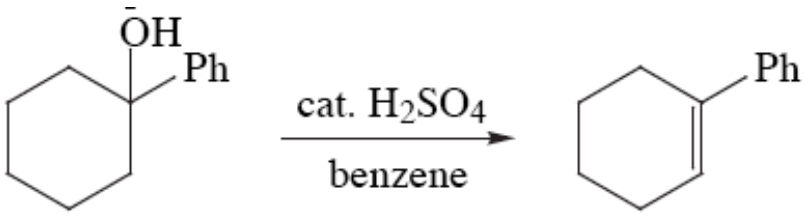
2. the solvent is saturated with a good, nonbasic nucleophile like Cl^-;



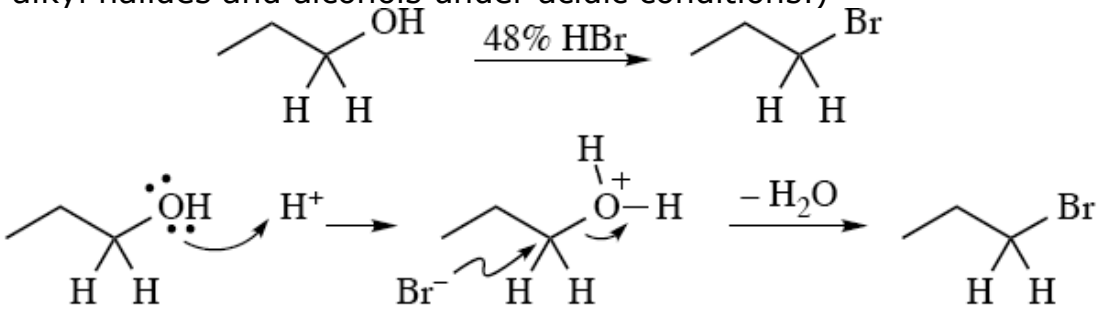
3. a nucleophile is in the same molecule as the electrophile and a five- or six-membered ring can form.



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!)



In summary:

Nature of Electrophile (X=OH, OR, or halogen)	Low concentration of nucleophile	High concentration of nucleophile
1° C(sp^3)–X	N. R.	S_N2 with conc. HX
2° C(sp^3)–X	E1	S_N1
3° C(sp^3)–X	E1	S_N1

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.

7.6.3. Neutral Conditions.

Sometimes the reaction conditions are not obviously acidic or basic, and it is not clear whether one should look for an S_N1, S_N2, E1, or E2 mechanism. In this case look for the following clues:

• Is there a good nucleophile/poor base, such as a phosphine R_3P or a thioether R_2S, and an alkyl halide (not alcohol)? If so, S_N2 subsitution may occur.
• Is there a 3° halide in a protic solvent? If so, an S_N1 reaction may occur. (Ionization of 3° halides to give the carbocations is very facile, especially in a protic solvent.)
• Is there a 2° or 3° halide in a polar aprotic solvent? If so, an E1 reaction may occur. (Ionization of 2° and 3° halides to give the carbocations is very facile in polar aprotic solvent.)

See, Jones figure 7.94 – for synthetic potential of substitution reactions