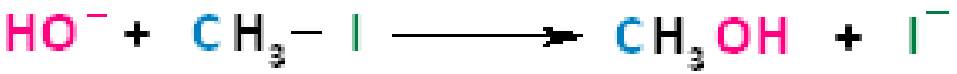
Nucleophilic Substitution Reactions:

Two types of nucleophilic substitution reactions. One type is referred to as unimolecular nucleophilic substitution (SN1), whereby the rate determining step is unimolecular and bimolecular nucleophilic substitution (SN2), whereby the rate determining step is bimolecular. We will begin our discussion with SN2 reactions, and discuss SN1 reactions later.

Biomolecular Nucleophilic Substitution Reactions and Kinetics

In the term SN2, the S stands for substitution, the N stands for nucleophilic, and the number two stands for bimolecular, meaning there are two molecules involved in the rate determining step. The rate of bimolecular nucleophilic substitution reactions depends on the concentration of both the haloalkane and the nucleophile. To understand how the rate depends on the concentrations of both the haloalkane and the nucleophile, let us look at the following example. The hydroxide ion is the nucleophile and methyl iodide is the haloalkane.



$$HO^- + CH_3-I \longrightarrow CH_3OH + I^-$$

$$\text{Rate} = k[CH_3-I][HO^-]$$

If we were to double the concentration of either the haloalkane or the nucleophile, we can see that the rate of the reaction would proceed twice as fast as the initial rate.

$$\text{Rate}_1 = k[CH_3-I][HO^-]$$

$$\text{Rate}_2 = 2k[CH_3-I][HO^-]$$

$$\text{Rate}_2 = 2\,\text{Rate}_1$$

If we were to double the concentration of both the haloalkane and the nucleophile, we can see that the rate of the reaction would proceed four times as fast as the initial rate.

$$\text{Rate}_1 = k[CH_3-I][HO^-]$$

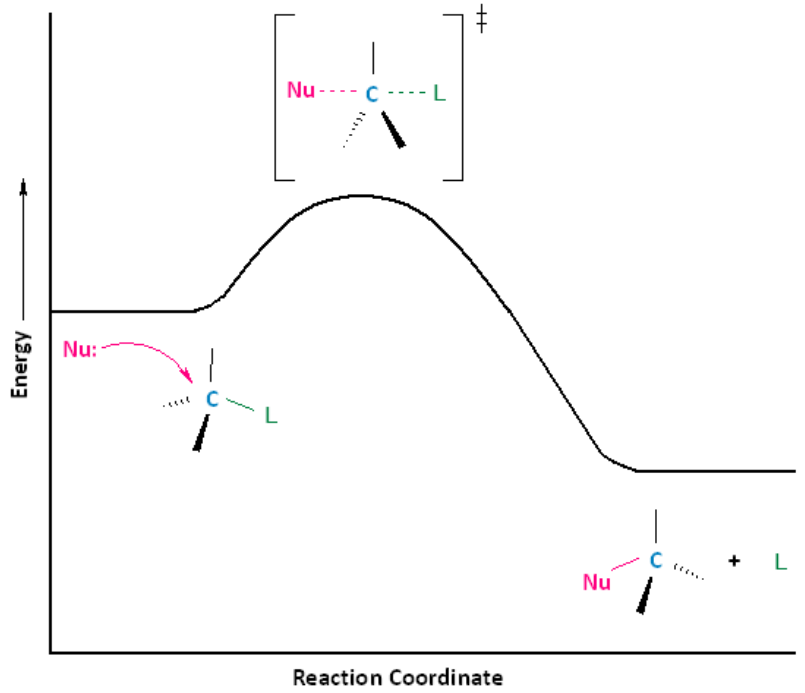
$$\text{Rate}_2 = 4k[CH_3-I][HO^-]$$

$$\text{Rate}_2 = 4\,\text{Rate}_1$$

Bimolecular Nucleophilic Substitution Reactions Are Concerted

Bimolecular nucleophilic substitution (SN2) reactions are concerted, meaning they are a one step process. This means that the process whereby the nucleophile attacks and the leaving group leaves is simultaneous. Hence, the bond-making between the nucleophile and the electrophilic carbon occurs at the same time as the bond-breaking between the electrophilic carbon and the leaving group.

The potential energy diagram for an S_N2 reaction is shown below. Upon nucleophilic attack, a single transition state is formed. A transition state, unlike a reaction intermediate, is a very short-lived species that cannot be isolated or directly observed. Again, this is a single-step, concerted process with the occurrence of a single transition state.



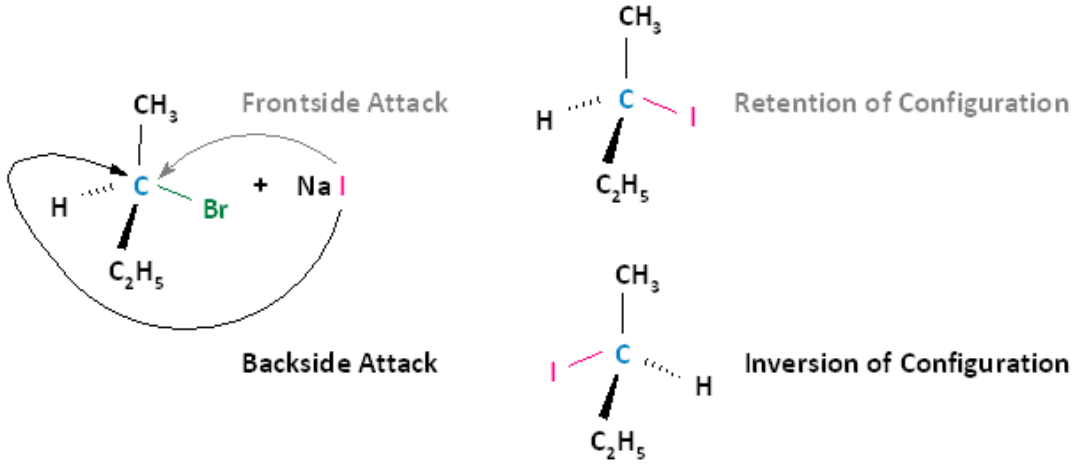
Frontside vs. Backside Attacks

A biomolecular nucleophilic substitution (SN2) reaction is a type of nucleophilic substitution whereby a lone pair of electrons on a nucleophile attacks an electron deficient electrophilic center and bonds to it, resulting in the expulsion of a leaving group. It is possible for the nucleophile to attack the electrophilic center in two ways.

Frontside Attack: In a frontside attack, the nucleophile attacks the electrophilic center on the same side as the leaving group. When a frontside attack occurs, the stereochemistry of the product remains the same; that is, we have retention of configuration.

Backside Attack: In a backside attack, the nucleophile attacks the electrophilic center on the side that is opposite to the leaving group. When a backside attack occurs, the stereochemistry of the product does not stay the same. There is inversion of configuration.

The following diagram illustrates these two types of nucleophilic attacks, where the frontside attack results in retention of configuration; that is, the product has the same configuration as the substrate. The backside attack results in inversion of configuration, where the product's configuration is opposite that of the substrate.

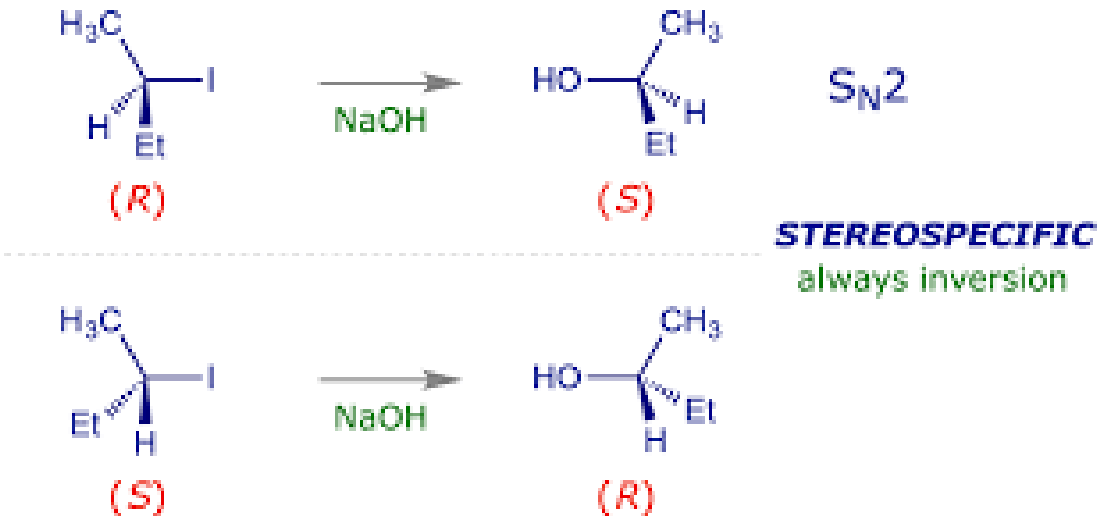


Experimental Observation: All SN2 Reactions Proceed With Nucleophilic Backside Attacks

Experimental observation shows that all SN2 reactions proceed with inversion of configuration; that is, the nucleophile will always attack from the backside in all SN2 reactions. To think about why this might be true, remember that the nucleophile has a lone pair of electrons to be shared with the electrophilic center, and the leaving group is going to take a lone pair of electrons with it upon leaving. Because like charges repel each other, the nucleophile will always proceed by a backside displacement mechanism.

SN2 Reactions Are Stereospecific

The SN2 reaction is stereospecific. A stereospecific reaction is one in which different stereoisomers react to give different stereoisomers of the product. For example, if the substrate is an R enantiomer, a frontside nucleophilic attack results in retention of configuration, and the formation of the R enantiomer. A backside nucleophilic attack results in inversion of configuration, and the formation of the S enantiomer **(subject to the nature and priority order of the leaving group or nucleophile)**.

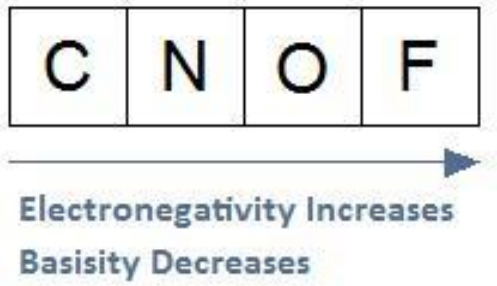


Four Factors to Consider in Determining the Relative Ease at Which SN2 Displacement Occurs
The nature of the leaving group (SN2 Reactions-The Leaving Group)
The reactivity of the nucleophile (SN2 Reactions-The Nucleophile)
The solvent (SN2 Reactions-The Nucleophile)
The structure of the alkyl portion of the substrate (SN2 Reactions-The Substrate)

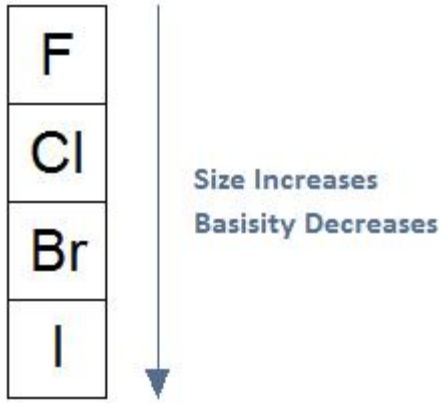
The Nature of the Leaving Group

In order to understand the nature of the leaving group, it is important to first discuss factors that help determine whether a species will be a strong base or weak base. If you remember from general chemistry, a Lewis base is defined as a species that donates a pair of electrons to form a covalent bond. The factors that will determine whether a species wants to share its electrons or not include electronegativity, size, and resonance.

As Electronegativity Increases, Basicity Decreases: In general, if we move from the left of the periodic table to the right of the periodic table as shown in the diagram below, electronegativity increases. As electronegativity increases, basicity will decrease, meaning a species will be less likely to act as base; that is, the species will be less likely to share its electrons.



As Size Increases, Basicity Decreases: In general, if we move from the top of the periodic table to the bottom of the periodic table as shown in the diagram below, the size of an atom will increase. As size increases, basicity will decrease, meaning a species will be less likely to act as a base; that is, the species will be less likely to share its electrons.



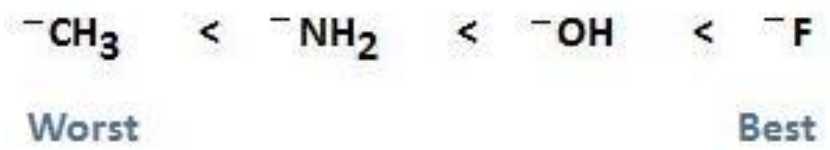
Resonance Decreases Basicity: The third factor to consider in determining whether or not a species will be a strong or weak base is resonance. As you may remember from general chemistry, the formation of a resonance stabilized structure results in a species that is less willing to share its electrons. Since strong bases, by definition, want to share their electrons, resonance stabilized structures are weak bases.

Weak Bases are the Best Leaving Groups

Now that we understand how electronegativity, size, and resonance affect basicity, we can combine these concepts with the fact that weak bases make the best leaving groups. Think about why this might be true. In order for a leaving group to leave, it must be able to accept electrons. A strong bases wants to donate electrons; therefore, the leaving group must be a weak base. We will now revisit electronegativity, size, and resonance, moving our focus to the leaving group, as well providing actual examples.

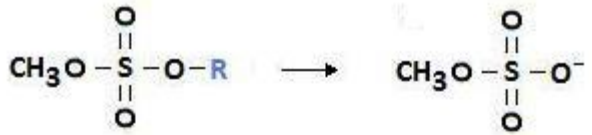
As Electronegativity Increases, The Ability of the Leaving Group to Leave Increases.

As mentioned previously, if we move from left to right on the periodic table, electronegativity increases. With an increase in electronegativity, basisity decreases, and the ability of the leaving group to leave increases. This is because an increase in electronegativity results in a species that wants to hold onto its electrons rather than donate them. The following diagram illustrates this concept, showing -CH3 to be the worst leaving group and F- to be the best leaving group. This particular example should only be used to facilitate your understanding of this concept. In real reaction mechanisms, these groups are not good leaving groups at all. For example, fluoride is such a poor leaving group that SN2 reactions of fluoroalkanes are rarely observed.



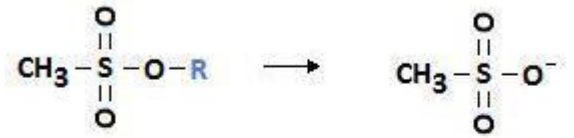
As Size Increases, The Ability of the Leaving Group to Leave Increases: Here we revisit the effect size has on basicity. If we move down the periodic table, size increases. With an increase in size, basicity decreases, and the ability of the leaving group to leave increases. The relationship among the following halogens, unlike the previous example, is true to what we will see in upcoming reaction mechanisms.

F	<	Cl	<	Br	<	I
Worst		Fair		Good		Excellent

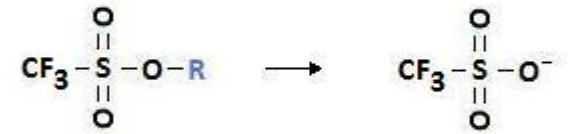


Methyl Sulfate Ion

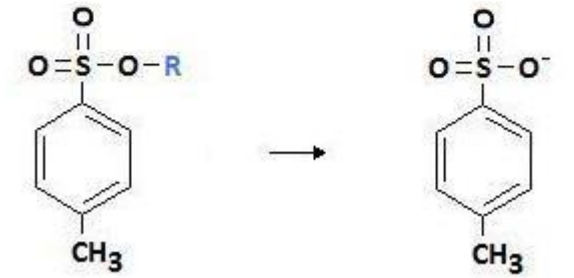
Resonance Increases the Ability of the Leaving Group to Leave: As we learned previously, resonance stabilized structures are weak bases. Therefore, leaving groups that form resonance structures upon leaving are considered to be excellent leaving groups. The following diagram shows sulfur derivatives of the type ROSO3- and RSO3-. Alkyl sulfates and sulfonates like the ones shown make excellent leaving groups. This is due to the formation of a resonance stabilized structure upon leaving.



Methanesulfonate Ion (Mesylate)



Trifluoromethanesulfonate Ion (Triflate Ion)



4-Methylbenzenesulfonate Ion (Tosylate)

The Reactivity of the Nucleophile

Now that we have determined what will make a good leaving group, we will now consider nucleophilicity. That is, the relative strength of the nucleophile. Nucleophilicity depends on many factors, including charge, basicity, solvent, polarizability, and the nature of the substituents.

Increasing the Negative Charge Increases Nucleophilicity

Nucleophiles can be neutral or negatively charged. In either case, it is important that the nucleophile be a good Lewis base, meaning it has electrons it wants to share. The following diagram is just a reminder of some of the nucleophiles that were presented in the section covering nucleophilic substitution. In looking at these two types of nucleophiles, you should notice that a reactive atom, such as oxygen, in a neutral species can also be a reactive atom in a negatively charged species. For example, the O in OH- is negatively charged, but the O in H2O is neutral.

Neutral Nucleophiles

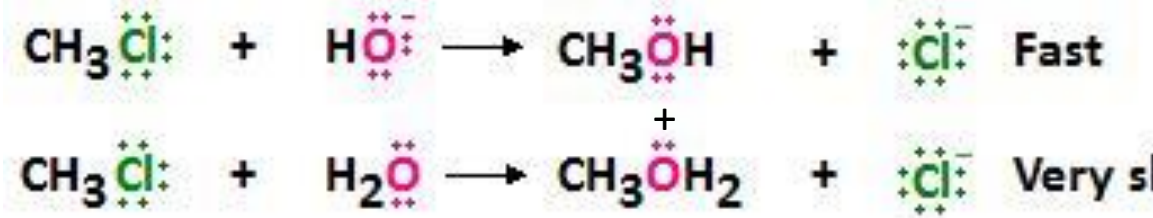
H_2O, NH_3, RNH_2, R_2NH, R_3N, ROH, RCOOH, RSH, and PR_3

Charged Nucleophiles

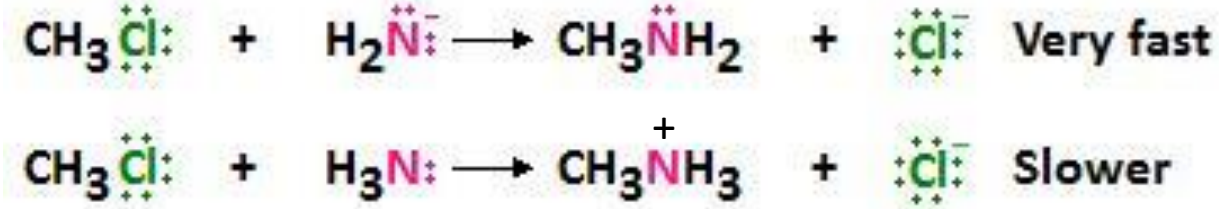
RO^-, $^-NH_2$, $R\bar{N}H$, R_2N^-, HS^-, RS^-, RSe^-, Cl^-, Br^-, I^-, F^-, CN^-, ^-OH, RCO_2^-

It has been experimentally shown that a nucleophile containing a negatively charged reactive atom is better than a nucleophile containing a reactive atom that is neutral. The next diagram illustrates this concept. Notice that when oxygen is part of the hydroxide ion, it bears a negative charge, and when it is part of a water molecule, it is neutral. The O of -OH is a better nucleophile than the O of H2O, and results in a faster reaction rate. Similarly, when nitrogen is part of NH2, it bears a negative charge, and when it is part of NH3, it is neutral. The N of NH2 is a better nucleophile than the N of NH3, and results in a faster reaction rate.

Experiment #1

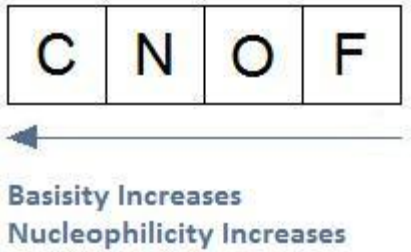


Experiment #2

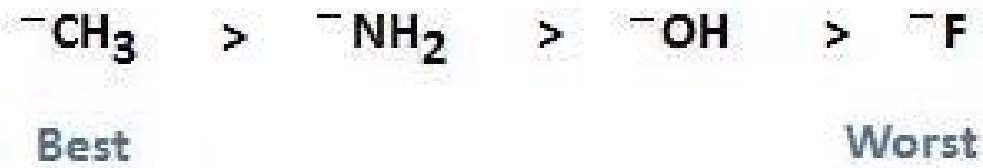


When Moving Across a Row, Nucleophilicity Follows basicity

To say that nucleophilicity follows basicity across a row means that, as basicity increases from right to left on the periodic table, nucleophilicity also increases. As basicity decreases from left to right on the periodic table, nucleophilicity also decreases. When it comes to nucleophilicity, do not assign this same rule when making comparisons between the halogens located in a column. In this case of moving up and down a column, nucleophilicity does not always follow basicity. It depends on the type of solvent you are using.



In the section Nucleophilic Substitution, we assigned a relationship to leaving groups containing C, N, O, and F, showing that the strength of the leaving group follows electronegativity. This is based on the fact that the best leaving groups are those that are weak bases that do not want to share their electrons. The best nucleophiles however, are good bases that want to share their electrons with the electrophilic carbon. The relationship shown below, therefore, is the exact opposite of that shown for the strength of a leaving group.

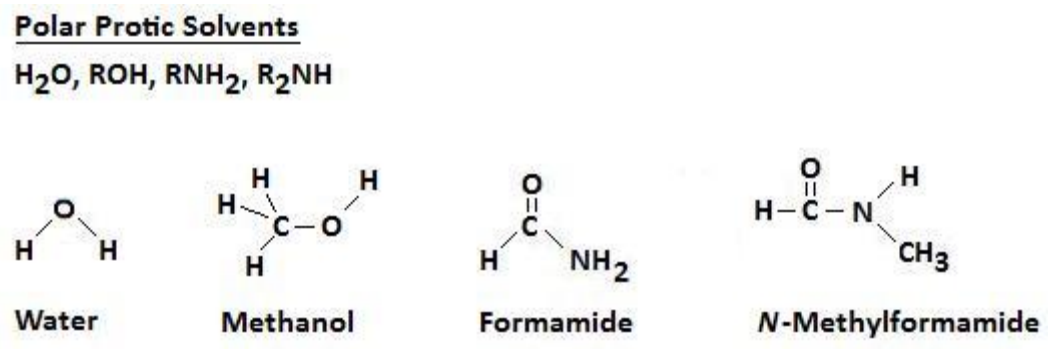


Solvents and Nucleophilicity

In general chemistry, we classified solvents as being either polar or nonpolar. Polar solvents can be further subdivided into protic and and aprotic solvents.

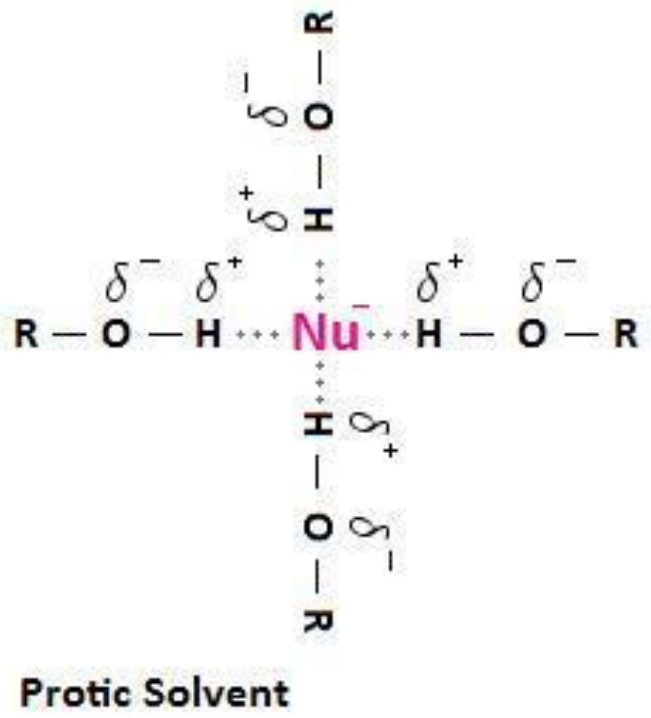
Protic Solvents

A protic solvent is a solvent that has a hydrogen atom bound to an oxygen or nitrogen. A few examples of protic solvents include H2O, ROH, RNH2, and R2NH, where water is an example of an inorganic protic solvent, and alcohols and amides are examples of organic solvents. The diagram below shows a few examples of protic solvents we will see.



Since oxygen and nitrogen are highly electronegative atoms, the O-H and N-H bonds that are present in protic solvents result in a hydrogen that is positively polarized. When protic solvents are used in nucleophilic substitution reactions, the positively polarized hydrogen of the solvent molecule can interact with the negatively charged nucleophile. In solution, molecules or ions that are surrounded by these solvent molecules are said to be **solvated**. Solvation is the process of attraction and association of solvent molecules with ions of a solute. The solute, in this case, is a negatively charged nucleophile.

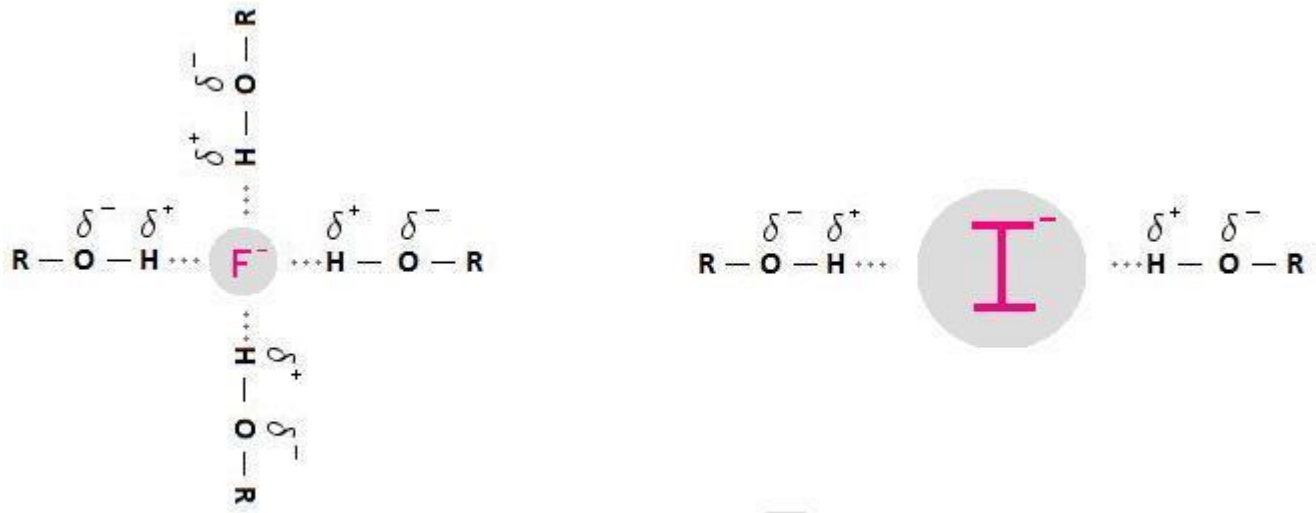
The following diagram depicts the interaction that can occur between a protic solvent and a negatively charged nucleophile. The interactions are called **hydrogen bonds**. A hydrogen bond results from a from a dipole-dipole force between between an electronegative atom, such as a halogen, and a hydrogen atom bonded to nitrogen, oxygen or fluorine. In the case below, we are using an alcohol (ROH) as an example of a protic solvent, but be aware that this interaction can occur with other solvents containing a positively polarized hydrogen atom, such as a molecule of water, or amides of the form RNH_2 and R_2NH.



Protic Solvent

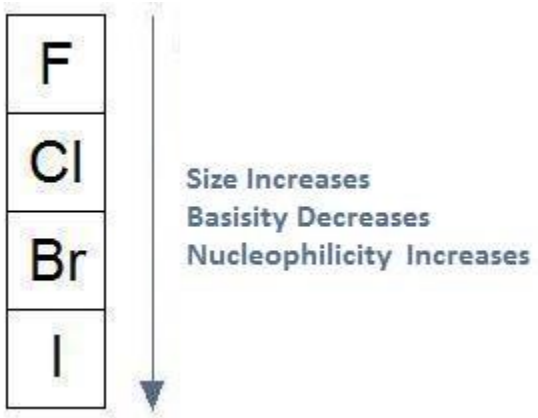
Why is this important? Solvation weakens the nucleophile; that is, solvation decreases nucleophilicity. This is because the solvent forms a "shell" around the nucleophile, impeding the nucleophile's ability to attack an electrophilic carbon. Furthermore, because the charge on smaller anions is more concentrated, small anions are more tightly solvated than large anions.

The picture below illustrates this concept. Notice how the smaller fluoride anion is represented as being more heavily solvated than the larger iodide anion. This means that the fluoride anion will be a weaker nucleophile than the iodide anion. In fact, it is important to note that fluoride will not function as a nucleophile at all in protic solvents. It is so small that solvation creates a situation whereby fluoride's lone pair of electrons are no longer accessible, meaning it is unable to participate in a nucleophilic substitution reaction.



Protic Solvent

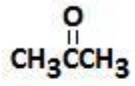
Previously we learned how nucleophilicity follows basicity when moving across a row. In our discussion on the effect of protic solvents on nucleophilicity, we learned that solvation weakens the nucleophile, having the greatest effect on smaller anions. In effect, when using protic solvents, nucleophilicity does not follow basicity when moving up and down a column. In fact, it's the exact opposite: when basicity decreases, nucleophilicity increases and when basicity increases, nucleophilicity decreases.

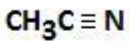


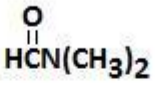
Aprotic Solvents

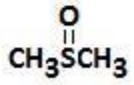
An aprotic solvent is a solvent that lacks a positively polarized hydrogen. The next diagram illustrates several polar aprotic solvents that you should become familiar with.

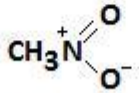
Polar Aprotic Solvents

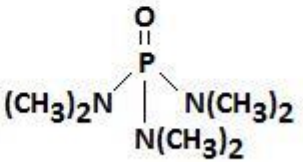

Acetone


Ethanenitrile (Acetonitrile)


N,N -Dimethylformamide (DMF)

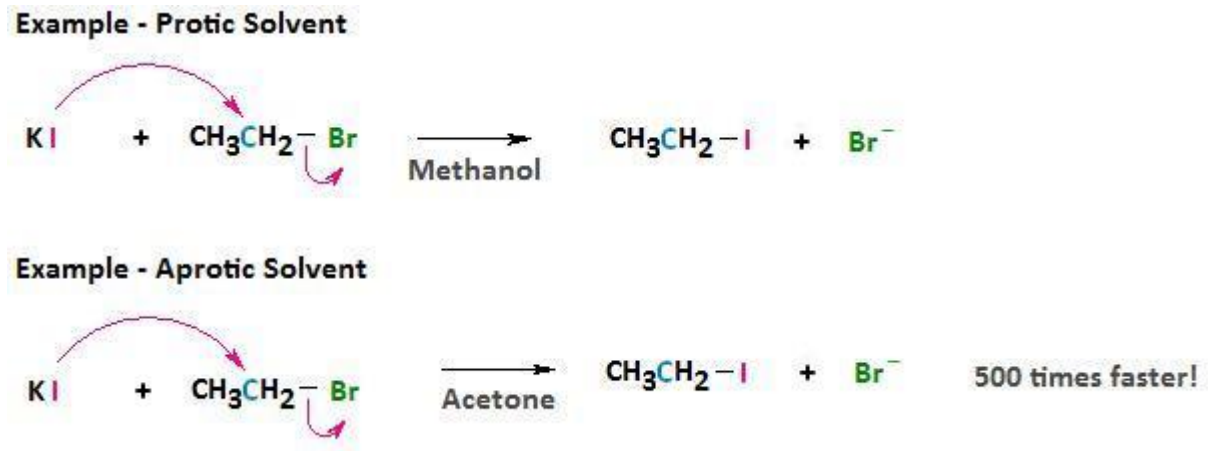

Dimethyl sulfoxide (DMSO)


Nitromethane


Hexamethylphosphoric triamide (HMPA)

Aprotic solvents, like protic solvents, are polar but, because they lack a positively polarized hydrogen, they do not form hydrogen bonds with the anionic nucleophile. The result, with respect to solvation, is a relatively weak interaction between the aprotic solvent and the nucleophile.

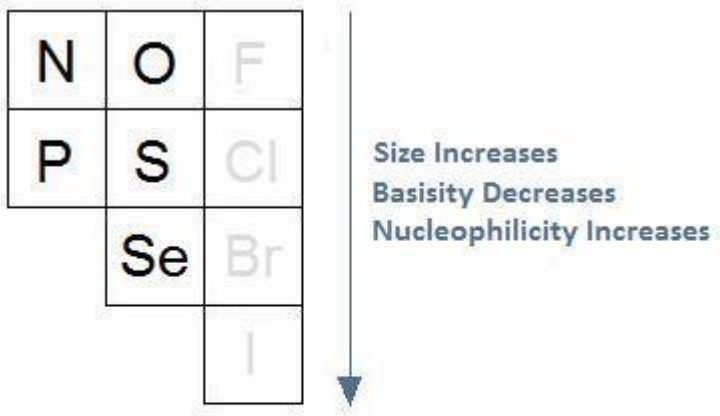
The consequence of this weakened interaction is two-fold. First, by using an aprotic solvent we can raise the reactivity of the nucleophile. This can sometimes have dramatic effects on the rate at which a nucleophilic substitution reaction can occur. For example, if we consider the reaction between bromoethane and potassium iodide, the reaction occurs 500 times faster in acetone than in methanol.



Increasing Atomic Size Increases Nucleophilicity

Thus far, our discussion on nucleophilicity and solvent choice has been limited to negatively charged nucleophiles, such as F^-, Cl^-, Br^-, and I^-. With respect to these anions we learned that, when using protic solvents, nucleophilicity does not follow basicity, and when using aprotic solvents, the same relationship can occur, or there could be an inversion in the order of reactivity.

What happens as we move up and down a column when considering *uncharged nucleophiles*? It turns out that, in the case of uncharged nucleophiles, size dictates nucleophilicity. This is because larger elements have bigger, more diffuse, and more polarizable electron clouds. This cloud facilitates the formation of a more effective orbital overlap in the transition state of bimolecular nucleophilic substitution (SN_2) reactions, resulting in a transition state that is lower in energy and a nucleophilic substitution that occurs at a faster rate.



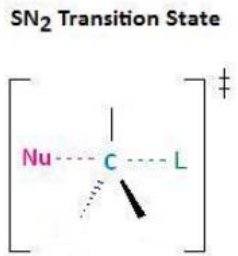
Examples of Uncharged Nucleophiles

$H_2Se > H_2S > H_2O$

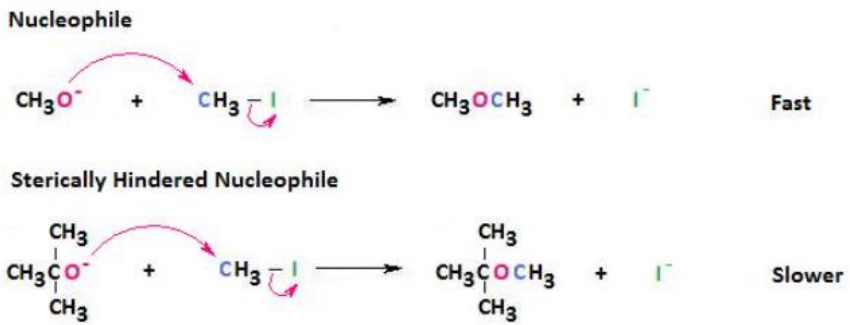
$PH_3 > NH_3$

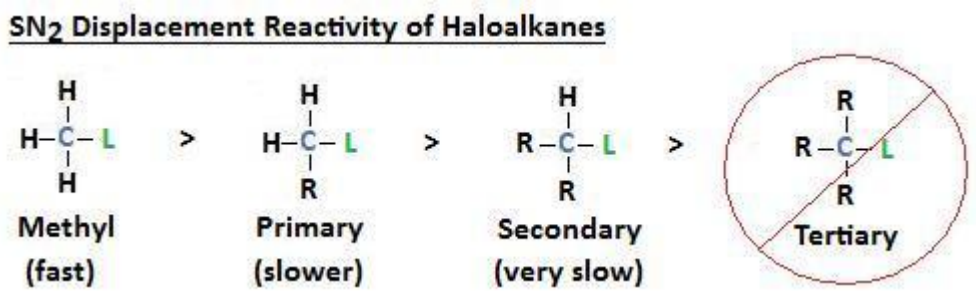
Sterically Hindered Nucleophiles React More Slowly

In the section Kinetics of Nucleophilic Substitution Reactions, we learned that the SN_2 transition state is very crowded. Recall that there are a total of 5 groups around the electrophilic center.



For this reason, sterically hindered nucleophiles react more slowly than those lacking steric bulk.

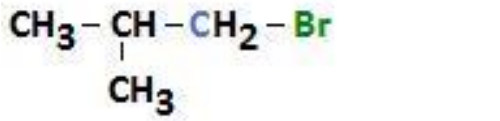




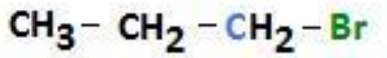
Substitutes on Neighboring Carbons Slow Nucleophilic Substitution Reactions

Previously we learned that adding R groups to the electrophilic carbon results in nucleophilic substitution reactions that occur at a slower rate. What if R groups are added to neighboring carbons? It turns out that the addition of substitutes on neighboring carbons will slow nucleophilic substitution reactions as well.

In the example below, 2-methyl-1-bromopropane differs from 1-bromopropane in that it has a methyl group attached to the carbon that neighbors the electrophilic carbon. The addition of this methyl group results in a significant decrease in the rate of a nucleophilic substitution reaction.



2-methyl-1-bromopropane



1-bromopropane

If R groups were added to carbons farther away from the electrophilic carbon, we would still see a decrease in the reaction rate. However, branching at carbons farther away from the electrophilic carbon would have a much smaller effect.

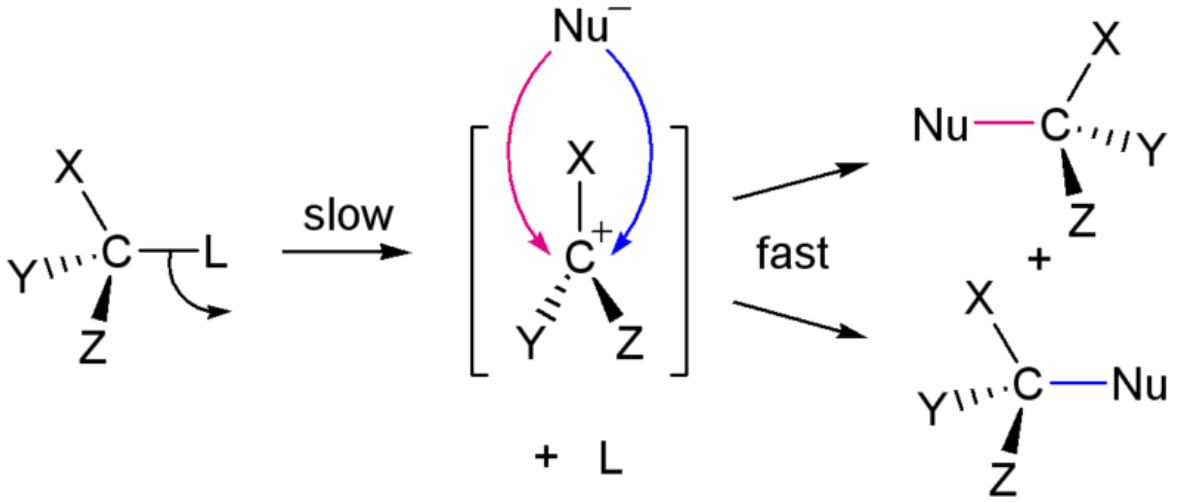
SN1 Reaction

In contrast to an SN2 reaction, in which the bond-making addition of the nucleophile and the bond-breaking departure of the leaving group occur in a single step, the SN1 reaction involves two separate steps: first the departure of the leaving group and then the addition of the nucleophile.

In the SN1 reaction, the bond between the substrate and the leaving group is broken when the leaving group departs with the pair of electrons that formerly composed the bond. As a result, the carbon atom to which the bond was formerly made is left with a positive charge. This positive charge on a carbon atom is called a carbocation, from "carbon" and "cation", the word for a positively charged atom. The formation of a carbocation is not energetically favored, so this step in the reaction is the slowest step and determines the overall rate of the reaction. The step which controls the overall rate of a reaction is called the rate-determining step.

Only after the leaving group has departed and a carbocation has formed, a nucleophile forms a bond to the carbocation, completing the substitution. This step is more energetically favorable and proceeds more quickly.

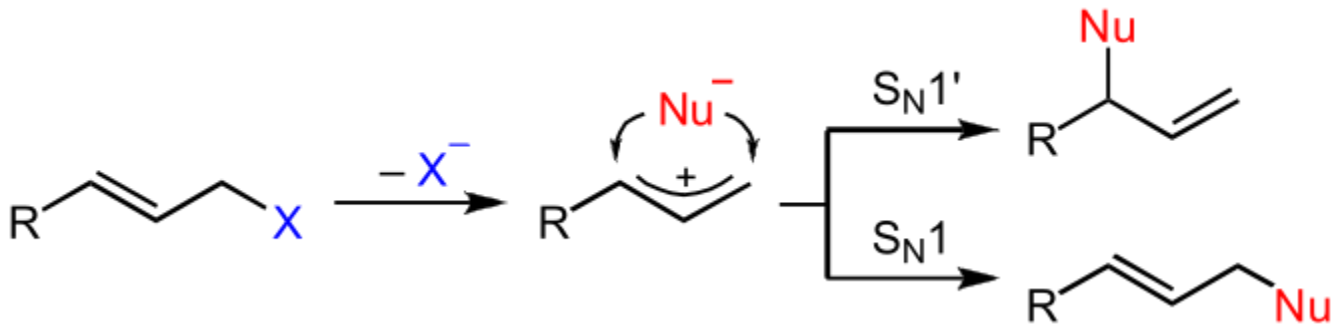
There are several important consequences to the unimolecular nature of the rate-determining step in the the SN1 reaction. First, since the rate is controlled by the loss of the leaving group and does not involve any participation of the nucleophile, the rate of the reaction is dependent only on the concentration of the substrate, not on the concentration of the nucleophile. Second, since the nucleophile attacks the carbocation only after the leaving group has departed, there is no need for back-side attack. The carbocation and its substituents are all in the same plane, meaning that the nucleophile can attack from either side. As a result, both enantiomers are formed in an the SN1 reaction, leading to a racemic mixture of both enantiomers. Finally, since the nucleophile does not participate in the rate-determining step, the strength of the nucleophile does not affect the rate of the SN1 reaction.



What factors govern the rate the probability of an SN1 reaction? The single most important factor is the stability of the carbocation. Alkyl substituents increase the stability of a carbocation, so increasing alkyl substitution of the carbon atom increases the probability of an SN1 reaction occurring.

Relative rate of SN1 reaction
Tertiary>Secondary>Primary>Methyl

Recall that, as in the case of an SN1 reaction, the above trend regarding degree of substitution is just a trend and the real factor that determines whether an SN1 reaction can occur is the stability of the carbocation. From above, we would expect an SN1 reaction not to occur at the site of a primary carbon atom. Indeed, such reactions do not occur in ordinary alkanes. However, in molecules in which the carbon next to the site of substitution contains a double bond, the SN1 reaction is possible. The reason is that the positive charge on the carbocation can be delocalized among multiple possible resonance structures (see Resonance and delocalization), making the carbocation dramatically more stable. This effect can occur when the carbon atom of interest is next to one double bond (allylic) or a benzene ring (benzylic). Note that in the allylic case, because of the delocalization of the positive charge, the nucleophile can attack at multiple sites this effect is absent in the benzylic case due to the need to preserve aromaticity. In summary, the key to the SN1 reaction is the stability of the carbocation.

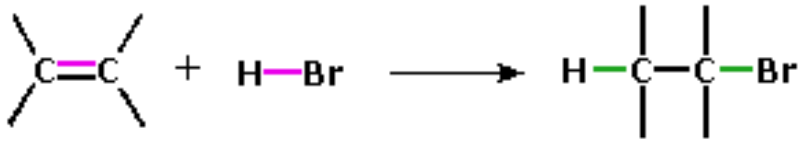


Addition Reactions

The most common chemical transformation of a carbon-carbon double bond is the addition reaction. A large number of reagents, both inorganic and organic, have been found to add to this functional group, and in this section we shall review many of these reactions.

1. Addition of Lewis Acids (Electrophilic Reagents)
2. Addition of Strong Brønsted Acids
3. Rearrangement of Carbocations

A large number of reagents, both inorganic and organic, have been found to add to this functional group, and in this section we shall review many of these reactions. A majority of these reactions are exothermic, due to the fact that the C-C pi-bond is relatively weak (ca. 63 kcal/mole) compared to the sigma-bonds formed with the atoms or groups of the reagent. Remember, the bond energies of a molecule are the energies required to break (homolytically) all the covalent bonds in the molecule. Consequently, if the bond energies of the product molecules are greater than the bond energies of the reactants, the reaction will be exothermic. The following calculations for the addition of H-Br are typical. Note that by convention exothermic reactions have a negative heat of reaction.



Heat of Reaction = 150.5 − 167.0 = −16.5 kcal/mole

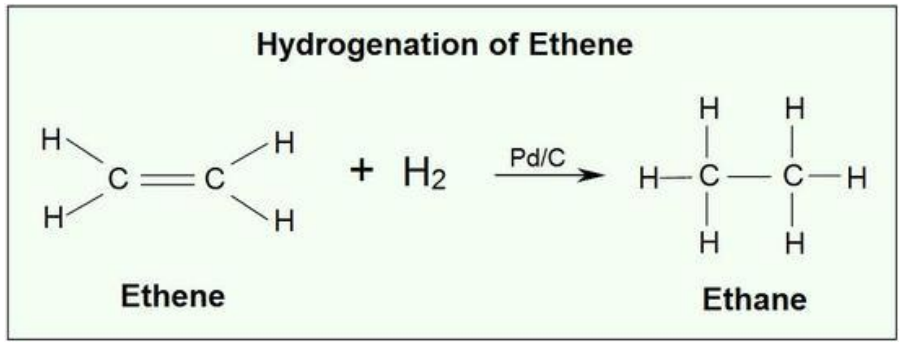
Bonds Broken: π C=C (63) & H–Br (87.5) **Sum = 150.5 kcal/mole**

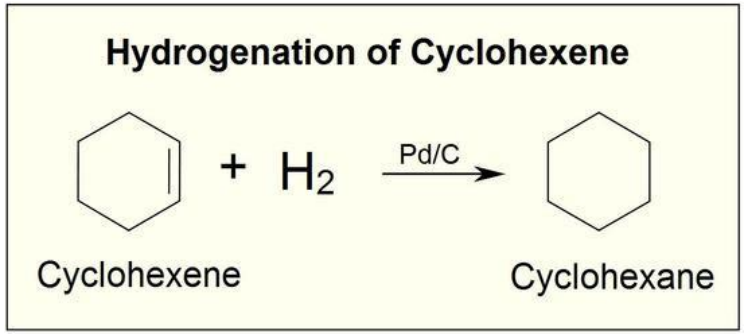
Bonds Formed: H–C (99) & Br–C (68) **Sum = 167.0 kcal/mole**

Addition of Hydrogen: Hydrogenation of Alkenes

Addition of hydrogen to a carbon-carbon double bond is called hydrogenation. The overall effect of such an addition is the reductive removal of the double bond functional group. Regioselectivity is not an issue, since the same group (a hydrogen atom) is bonded to each of the double bond carbons. The simplest source of two hydrogen atoms is molecular hydrogen (H2), but mixing alkenes with hydrogen does not result in any discernible reaction. Although the overall hydrogenation reaction is exothermic, a high activation energy prevents it from taking place under normal conditions. This restriction may be circumvented by the use of a catalyst,

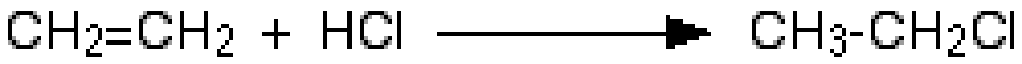
Ethene reacts with hydrogen in the presence of a finely divided palladium catalyst at a temperature of about 150°C. Ethane is produced.



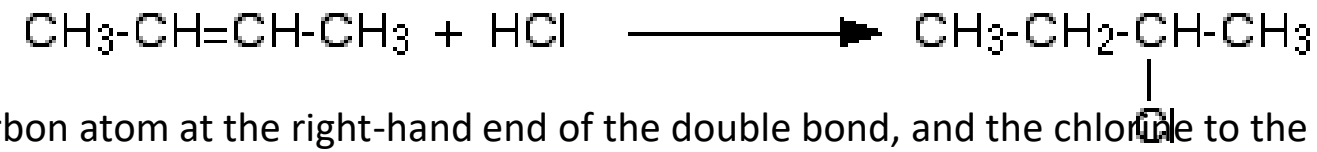


Addition of Hydrogen Halides to Alkenes

All alkenes undergo addition reactions with the hydrogen halides. A hydrogen atom joins to one of the carbon atoms originally in the double bond, and a halogen atom to the other. For example, with ethene and hydrogen chloride, you get chloroethane:



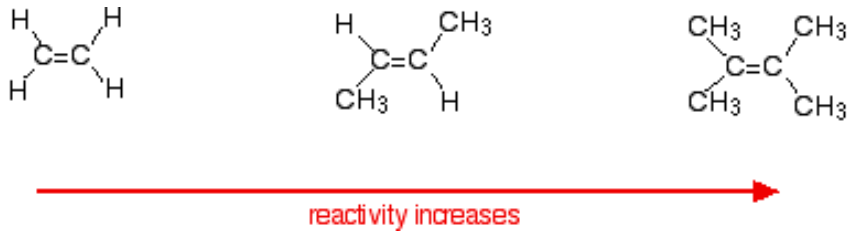
With but-2-ene you get 2-chlorobutane:



What happens if you add the hydrogen to the carbon atom at the right-hand end of the double bond, and the chlorine to the left-hand end? You would still have the same product. The chlorine would be on a carbon atom next to the end of the chain - you would simply have drawn the molecule flipped over in space. That would be different of the alkene was unsymmetrical - that's why we have to look at them separately.

Reaction rates increase in the order HF - HCl - HBr - HI. Hydrogen fluoride reacts much more slowly than the other three, and is normally ignored in talking about these reactions. When the hydrogen halides react with alkenes, the hydrogen-halogen bond has to be broken. The bond strength falls as you go from HF to HI, and the hydrogen-fluorine bond is particularly strong. Because it is difficult to break the bond between the hydrogen and the fluorine, the addition of HF is bound to be slow.

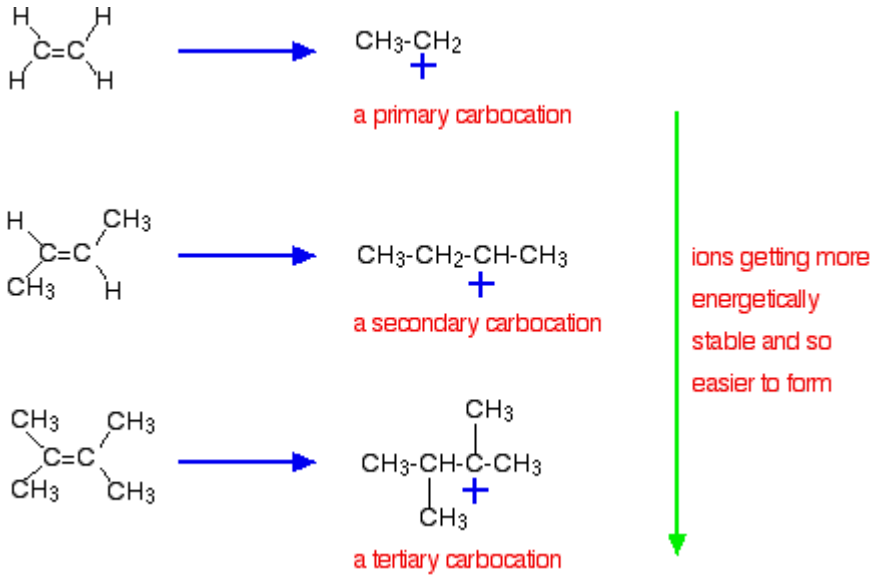
This applies to unsymmetrical alkenes as well as to symmetrical ones. For simplicity the examples given below are all symmetrical ones- but they don't have to be. Reaction rates increase as the alkene gets more complicated - in the sense of the number of alkyl groups (such as methyl groups) attached to the carbon atoms at either end of the double bond. For example:



There are two ways of looking at the reasons for this - both of which need you to know about the mechanism for the reactions.

Alkenes react because the electrons in the pi bond attract things with any degree of positive charge. Anything which increases the electron density around the double bond will help this. Alkyl groups have a tendency to "push" electrons away from themselves towards the double bond. The more alkyl groups you have, the more negative the area around the double bonds becomes. The more negatively charged that region becomes, the more it will attract molecules like hydrogen chloride.

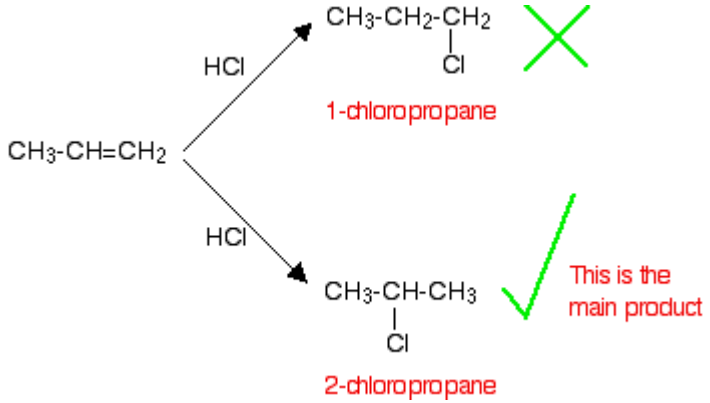
The more important reason, though, lies in the stability of the intermediate ion formed during the reaction. The three examples given above produce these carbocations (carbonium ions) at the half-way stage of the reaction:



The stability of the intermediate ions governs the activation energy for the reaction. As you go towards the more complicated alkenes, the activation energy for the reaction falls. That means that the reactions become faster.

Addition to unsymmetrical alkenes

In terms of reaction conditions and the factors affecting the rates of the reaction, there is no difference whatsoever between these alkenes and the symmetrical ones described above. The problem comes with the orientation of the addition - in other words, which way around the hydrogen and the halogen add across the double bond. If HCl adds to an unsymmetrical alkene like propene, there are two possible ways it could add. However, in practice, there is only one major product.

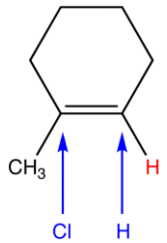


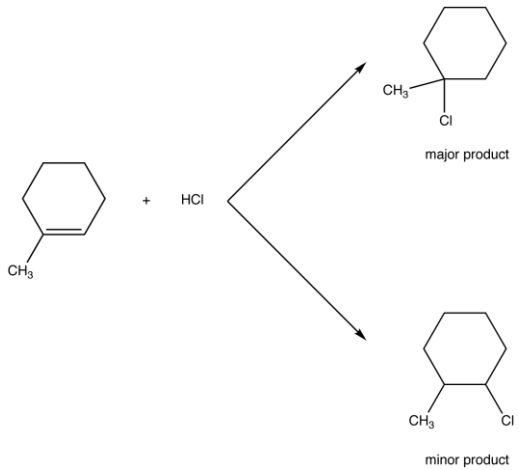
Definition: Markovnikov's Rule

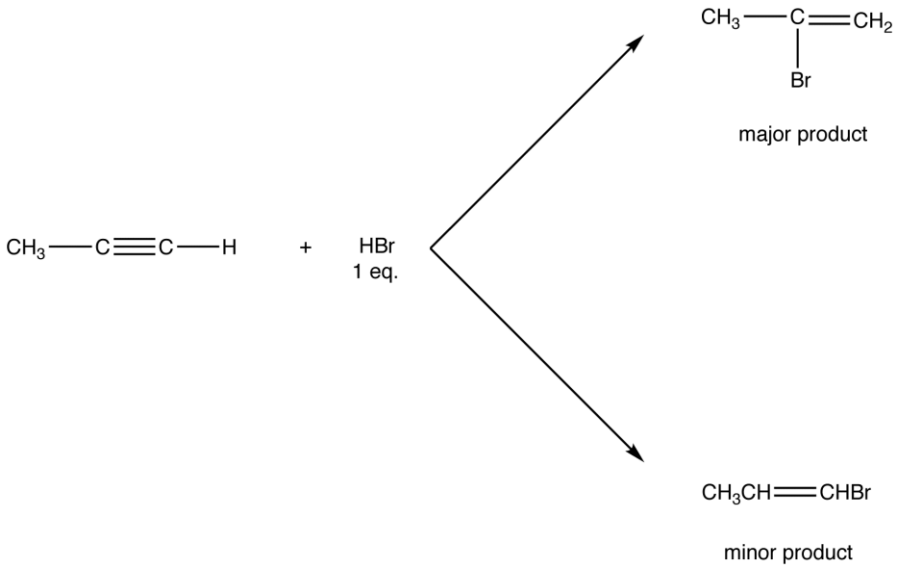
When a compound HX is added to an unsymmetrical alkene, the hydrogen becomes attached to the carbon with the most hydrogens attached to it already.

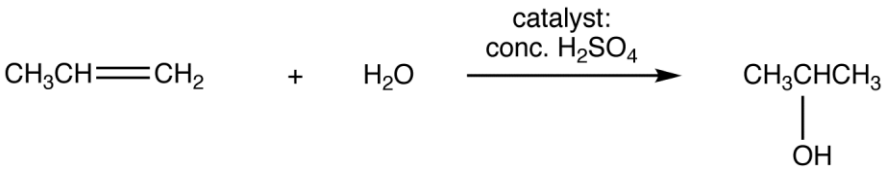
In this case, the hydrogen becomes attached to the CH2 group, because the CH2 group has more hydrogens than the CH group. Notice that only the hydrogens directly attached to the carbon atoms at either end of the double bond count. The ones in the CH3 group are totally irrelevant.

Although originally stated in relation to hydrohalogenation of unsymmetrical alkenes, Markovnikov's rule applies to some other electrophilic addition reactions of unsymmetrical alkenes (eg. 3) and to some electrophilic addition reactions of unsymmetrical alkynes









Radical Additions: Anti-Markovnikov Product Formation

Anti-Markovnikov rule describes the regiochemistry where the substituent is bonded to a less substituted carbon, rather than the more substitued carbon. This process is quite unusual, as carboncations which are commonly formed during alkene, or alkyne reactions tend to favor the more substitued carbon. This is because substituted carbocation allow more hyperconjugation and indution to happen, making the carbocation more stable.

This process was first explained by Morris Selig Karasch in his paper: 'The Addition of Hydrogen Bromide to Allyl Bromide' in 1933.1 Examples of Anti-Markovnikov includes Hydroboration-Oxidation and Radical Addition of HBr. A free radical is any chemical substance with unpaired electron. The more substituents the carbon is connected to, the more substituted is that carbon. For example: Tertiary carbon (most substituted), Secondary carbon (medium substituted), primary carbon (least substituted)

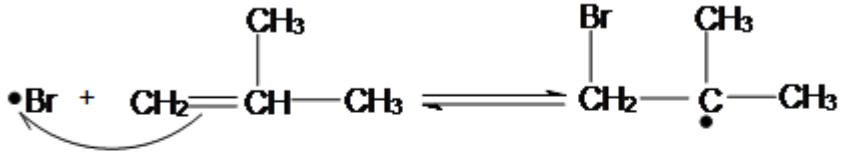
Anti-Markovnikov Radical Addition of Haloalkane can ONLY happen to HBr and there MUST be presence of Hydrogen Peroxide (H_2O_2). Hydrogen Peroxide is essential for this process, as it is the chemical which starts off the chain reaction in the initiation step. HI and HCl cannot be used in radical reactions, because in their radical reaction one of the radical reaction steps: Initiation is Endothermic, this means the reaction is unfavorable. To demonstrate the anti-Markovnikov regiochemistry, see example of 2-Methylprop-1-ene below:

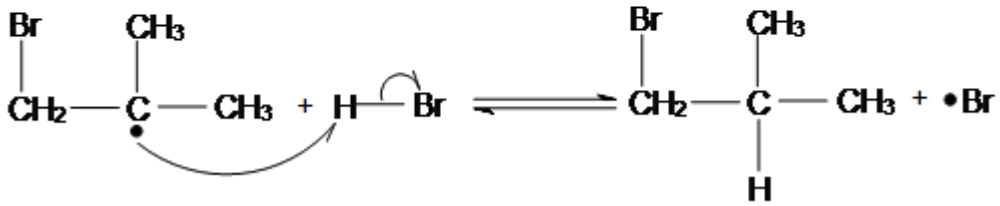
Initiation Steps

Hydrogen Peroxide is an unstable molecule, if we heat it, or shine it with sunlight, two free radicals of OH will be formed. These OH radicals will go on and attack HBr, which will take the Hydrogen and create a Bromine radical. Hydrogen radical do not form as they tend to be extremely unstable with only one electron, thus bromine radical which is more stable will be readily formed.

Propagation Steps

The Bromine Radical will go on and attack the LESS SUBSTITUTED carbon of the alkene. This is because after the bromine radical attacked the alkene a carbon radical will be formed. A carbon radical is more stable when it is at a more substituted carbon due to induction and hyperconjugation. Thus, the radical will be formed at the more substituted carbon, while the bromine is bonded to the less substituted carbon. After a carbon radical is formed, it will go on and attack the hydrogen of a HBr, which a bromine radical will be formed again.





Termination Steps

There are also Termination Steps, but we do not concern about the termination steps as they are just the radicals combining to create waste products. For example two bromine radical combined to give bromine. This radical addition of bromine to alkene by radical addition reaction will go on until all the alkene turns into bromoalkane, and this process will take some time to finish.

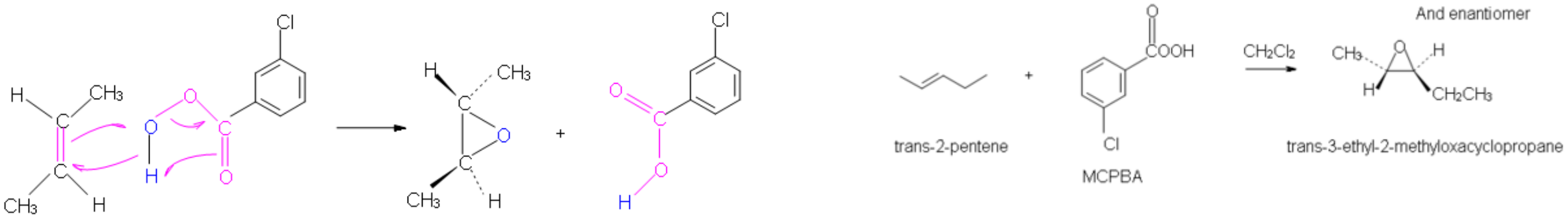
Oxidation of Alkenes - Epoxidation and Hydroxylation

Oxacyclopropane Synthesis by Peroxycarboxylic Acid

One way to oxidized a double bond is to produce an oxacyclopropane ring. Oxacyclopropane rings, also called epoxide rings, are useful reagents that may be opened by further reaction to form anti vicinal diols. One way to synthesize oxacyclopropane rings is through the reaction of an alkene with peroxycarboxylic acid. Oxacyclopropane synthesis by peroxycarboxylic acid requires an alkene and a peroxycarboxylic acid as well as an appropriate solvent. The peroxycarboxylic acid has the unique property of having an electropositive oxygen atom on the COOH group. The reaction is initiated by the electrophilic oxygen atom reacting with the nucleophilic carbon-carbon double bond. The mechanism involves a concerted reaction with a four-part, circular transition state. The result is that the originally electropositive oxygen atom ends up in the oxacyclopropane ring and the COOH group becomes COH.

Mechanism

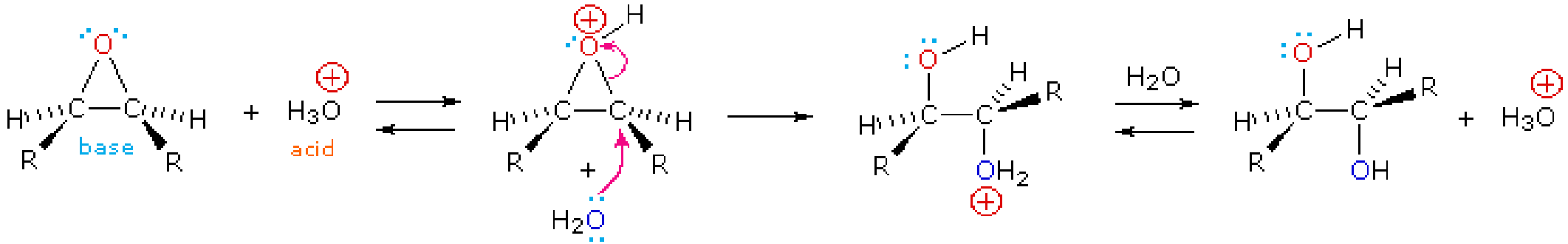
Peroxycarboxylic acids are generally unstable. An exception is meta-chloroperoxybenzoic acid, shown in the mechanism above. Often abbreviated MCPBA, it is a stable crystalline solid. Consequently, MCPBA is popular for laboratory use. However, MCPBA can be explosive under some conditions.



Peroxycarboxylic acids are sometimes replaced in industrial applications by monoperphthalic acid, or the monoperoxyphthalate ion bound to magnesium, which gives magnesium monoperoxyphthalate (MMPP). In either case, a nonaqueous solvent such as chloroform, ether, acetone, or dioxane is used. This is because in an aqueous medium with any acid or base catalyst present, the epoxide ring is hydrolyzed to form a vicinal diol, a molecule with two OH groups on neighboring carbons. (For more explanation of how this reaction leads to vicinal diols, see below.) However, in a nonaqueous solvent, the hydrolysis is prevented and the epoxide ring can be isolated as the product. Reaction yields from this reaction are usually about 75%. The reaction rate is affected by the nature of the alkene, with more nucleophilic double bonds resulting in faster reactions.

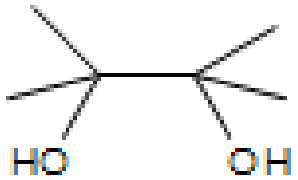
Anti Dihydroxylation

Epoxides may be cleaved by aqueous acid to give glycols that are often diastereomeric with those prepared by the syn-hydroxylation reaction described above. Proton transfer from the acid catalyst generates the conjugate acid of the epoxide, which is attacked by nucleophiles such as water in the same way that the cyclic bromonium ion described above undergoes reaction. The result is anti-hydroxylation of the double bond, in contrast to the syn-stereoselectivity of the earlier method. In the following equation this procedure is illustrated for a cis-disubstituted epoxide, which, of course, could be prepared from the corresponding cis-alkene. This hydration of an epoxide does not change the oxidation state of any atoms or groups.



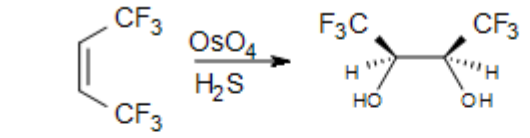
Syn Dihydroxylation

Osmium tetroxide oxidizes alkenes to give glycols through syn addition. A glycol, also known as a vicinal diol, is a compound with two -OH groups on adjacent carbons.

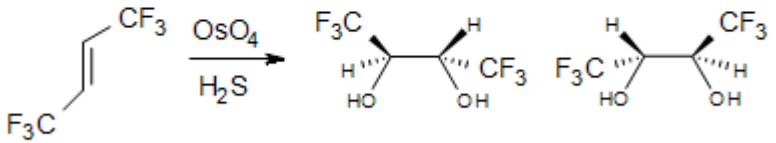


Introduction

The reaction with $OsO4$ is a concerted process that has a cyclic intermediate and no rearrangements. Vicinal syn dihydroxylation complements the epoxide-hydrolysis sequence which constitutes an anti dihydroxylation of an alkene. When an alkene reacts with osmium tetroxide, stereocenters can form in the glycol product. Cis alkenes give meso products and trans alkenes give racemic mixtures.



Cis **Meso**



Trans **Racemic Mixture**

$OsO4$ is formed slowly when osmium powder reacts with gasoues $O2$ at ambient temperature. Reaction of bulk solid requires heating to 400 °C:

$Os(s)+2O2(g)\rightarrow OS4(8.7.1)$

Since Osmium tetroxide is expensive and highly toxic, the reaction with alkenes has been modified. Catalytic amounts of $OsO4$ and stoichiometric amounts of an oxidizing agent such as hydrogen peroxide are now used to eliminate some hazards. Also, an older reagent that was used instead of $OsO4$ was potassium permanganate, $KMnO4$. Although syn diols will result from the reaction of $KMnO4$ and an alkene, potassium permanganate is less useful since it gives poor yields of the product because of overoxidation.

Mechanism

Electrophilic attack on the alkene

Pi bond of the alkene acts as the nucleophile and reacts with osmium (VIII) tetroxide (OsO_4)

2 electrons from the double bond flows toward the osmium metal

In the process, 3 electron pairs move simultaneously

Cyclic ester with Os (VI) is produced

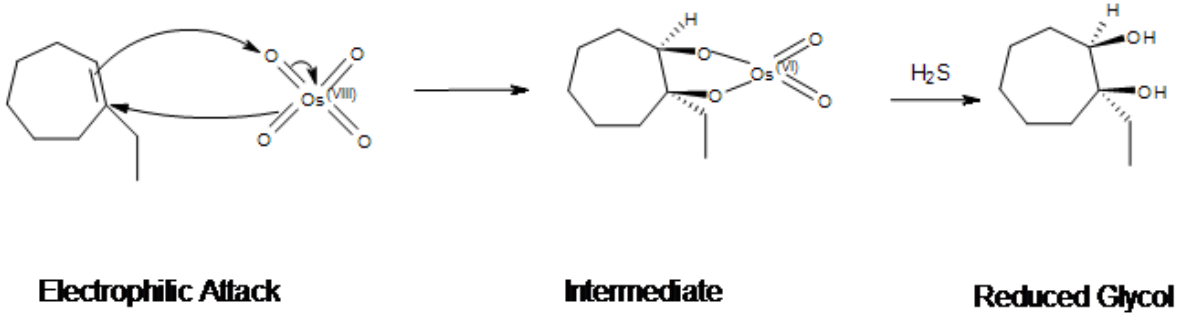
Reduction

H_2S reduces the cyclic ester

$NaHSO_4$ with H_2O may be used

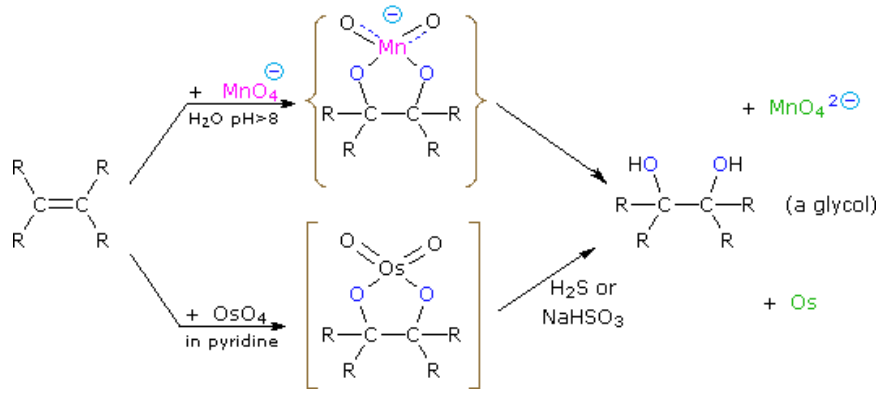
Forms the syn-1,2-diol (glycol)

Example: Dihydroxylation of 1-ethyl-1-cycloheptene



Hydroxylation of alkenes

Dihydroxylated products (glycols) are obtained by reaction with aqueous potassium permanganate (pH > 8) or osmium tetroxide in pyridine solution. Both reactions appear to proceed by the same mechanism (shown below); the metallocyclic intermediate may be isolated in the osmium reaction. In basic solution the purple permanganate anion is reduced to the green manganate ion, providing a nice color test for the double bond functional group. From the mechanism shown here we would expect syn-stereoselectivity in the bonding to oxygen, and regioselectivity is not an issue.



When viewed in context with the previously discussed addition reactions, the hydroxylation reaction might seem implausible. Permanganate and osmium tetroxide have similar configurations, in which the metal atom occupies the center of a tetrahedral grouping of negatively charged oxygen atoms. How, then, would such a species interact with the nucleophilic pi-electrons of a double bond? A possible explanation is that an empty d-orbital of the electrophilic metal atom extends well beyond the surrounding oxygen atoms and initiates electron transfer from the double bond to the metal, in much the same fashion noted above for platinum. Back-bonding of the nucleophilic oxygens to the antibonding π*-orbital completes this interaction. The result is formation of a metallocyclic intermediate, as shown.

Addition of Halogens: Halogenation of Alkenes

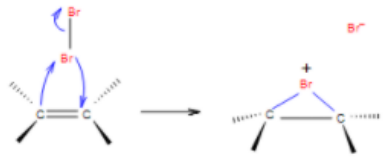
As halogen molecule, for example Br2, approaches a double bond of the alkene, electrons in the double bond repel electrons in bromine molecule causing polarization of the halogen bond. This creates a dipolar moment in the halogen molecule bond. Heterolytic bond cleavage occurs and one of the halogens obtains positive charge and reacts as an electrophile. The reaction of the addition is not regioselective but stereoselective.Stereochemistry of this addition can be explained by the mechanism of the reaction.In the first step electrophilic halogen with a positive charge approaches the double carbon bond and 2 p orbitals of the halogen, bond with two carbon atoms and create a cyclic ion with a halogen as the intermediate step. In the second step, halogen with the negative charge attacks any of the two carbons in the cyclic ion from the back side of the cycle as in the SN2 reaction. Therefore stereochemistry of the product is vicinial dihalides through anti addition.

Halogens that are commonly used in this type of the reaction are: Br and Cl . In thermodynamical terms I is too slow for this reaction because of the size of its atom, and F is too vigorous and explosive. Solvents that are used for this type of electrophilic halogenation are inert (e.g., CCl4) can be used in this reaction. Because halogen with negative charge can attack any carbon from the opposite side of the cycle it creates a mixture of steric products.

Electrophilic addition mechanism consists of two steps. Before constructing the mechanism let us summarize conditions for this reaction. We will use Br2 in our example for halogenation of ethylene.

Nucleophile	Double bond in alkene
Electrophile	Br_2, Cl_2
Regiochemistry	not relevant
Stereochemistry	**ANTI**

Step 1: In the first step of the addition the Br-Br bond polarizes, heterolytic cleavage occurs and Br with the positive charge forms a intermediate cycle with the double bond.

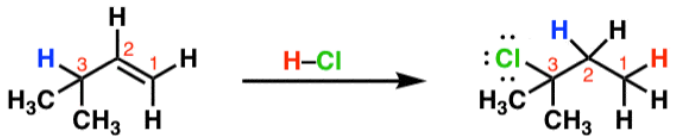


Step 2: In the second step, bromide anion attacks any carbon of the bridged bromonium ion from the back side of the cycle. Cycle opens up and two halogens are in the position **anti**.

Rearrangements in Alkene Addition Reactions

In exploring reactions that proceed along the carbocation pathway, every once in awhile you might see an example of an addition reaction that looks a little… strange. The alkene is gone, two new bonds have formed, but the positions of the new bonds is a little out of the ordinary. Like in this example!

An addition reaction with a twist

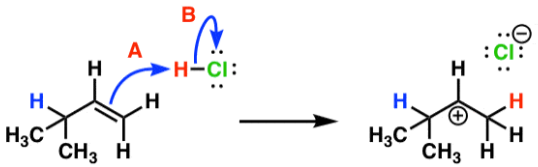


Form	Break
C_1–H	C_1–C_2 (π)
C_2–H	C_3–H
C_3–Cl	H–Cl

How did that chloride end up on C_3?

Hydride Shifts In Alkene Additions, Step 1: Attack Of Acid By The Nucleophile

Step 1 - attack of alkene on H–Cl (arrows A and B)



Form	Break
A C_1–H	A C_1–C_2 (π)
C_2–H	C_3–H
C_3–Cl	B H–Cl

Observation: secondary carbocation

The first step in this reaction we've seen before: attack of the alkene upon the electrophile (in this case, the H of H-Cl). The result is a carbocation.

Note that the carbocation that's been formed is a secondary carbocation, and it's adjacent to a tertiary carbon.

The Key Rearrangement Step: Hydride Shift

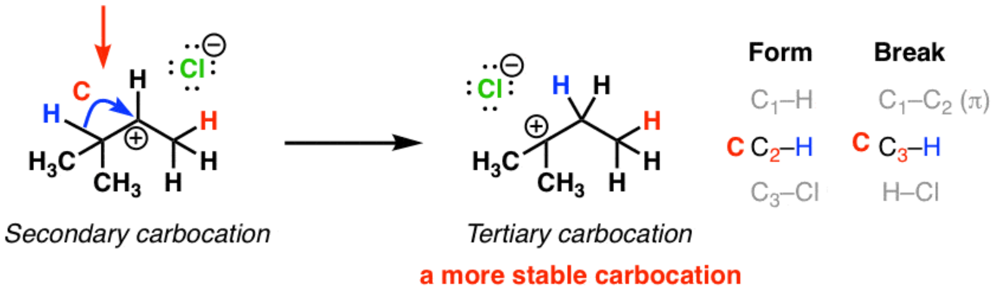
In this next step, the lone pair in the C-H bond migrates from the tertiary carbon to the secondary, forming a new (tertiary) carbocation. The driving force for this reaction is formation of the more stable carbocation.

Step 2 - rearrangement (arrow C)

Recall the order of carbocation stability: tertiary > secondary > primary

Migration of the C–H bond from C_3 to C_2 results in a more stable carbocation!

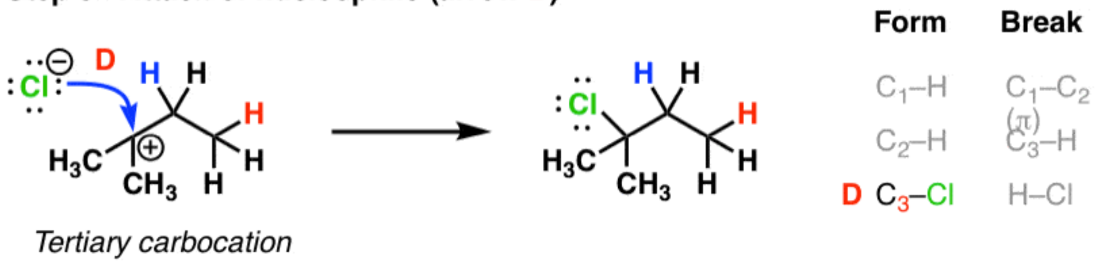
This arrow says, "break the C_3–H bond and form a new C_2–H bond"



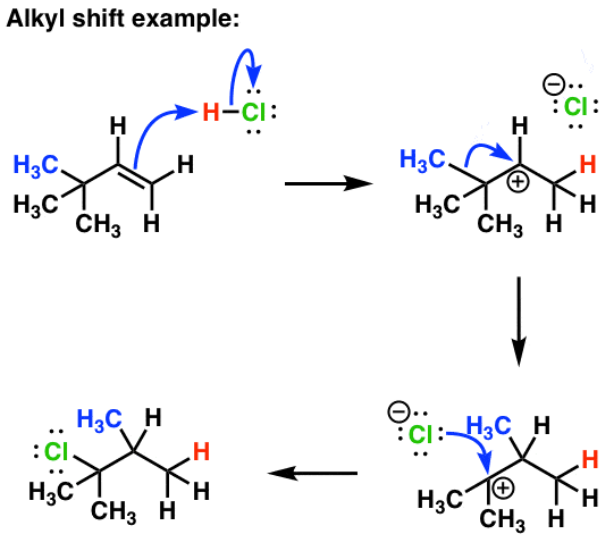
Note how it's just one arrow we're drawing here! The same arrow shows C-H bond breakage and C-H bond forming.

Step Three: Attack Of Nucleophile On The Carbocation

Step 3 - Attack of nucleophile (arrow D)

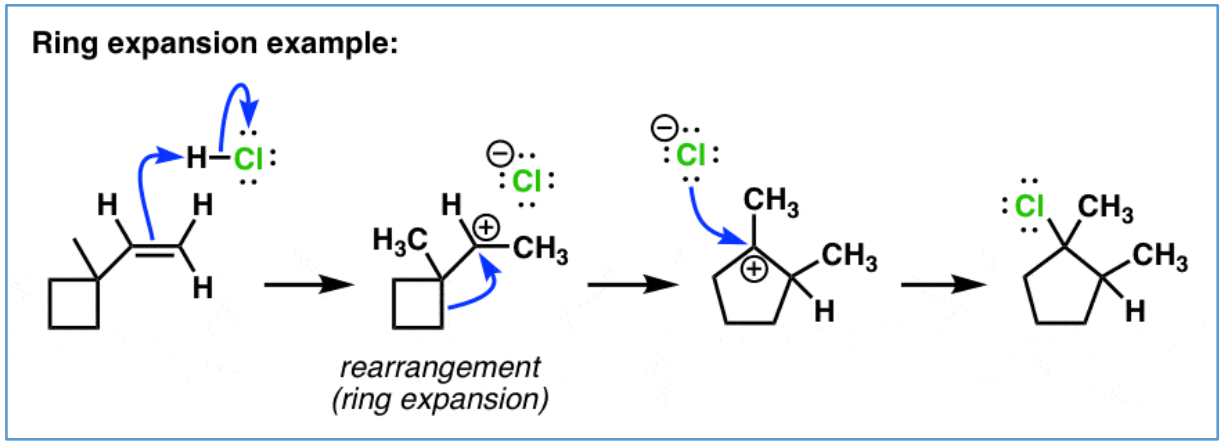


Alkene Addition Reactions With Alkyl Shifts



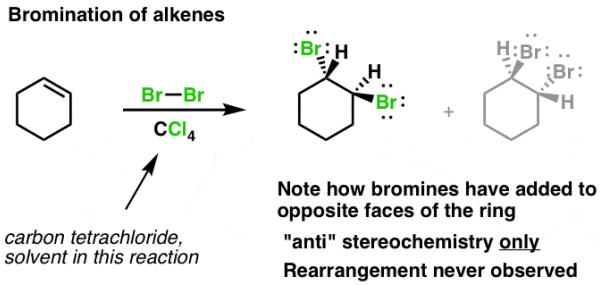
Rearrangements can also occur with alkyl shifts, as seen in the example below. Note again that the rearrangement step is represented by just one curved arrow!

Finally, one of the cases that students often find very difficult is in recognizing reactions that occur with rings (ring expansion or ring contraction). Although perhaps difficult to see, in fact it proceeds through exactly the same mechanism as in the cases above. Note again that we're depicting the rearrangement reaction with a single curved arrow.

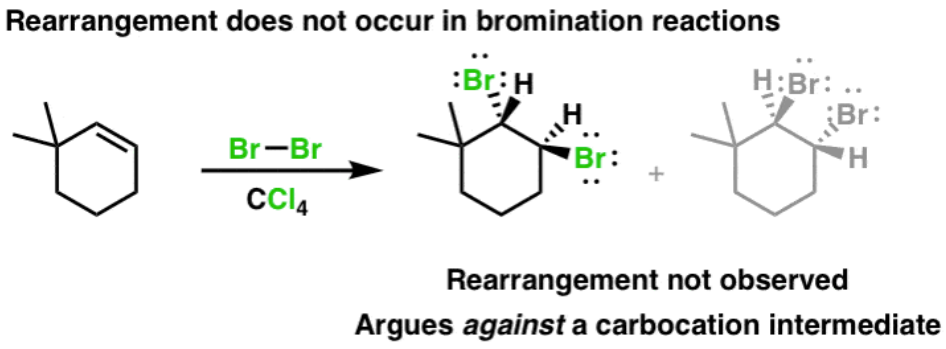


So why is it that the carbon from the ring migrates, and not the CH3 as before? A fair question. Migration of the CH3 would indeed produce a tertiary carbocation. However, migration of the CH2 from the ring not only produces a tertiary carbon but incrases the size of the ring from 4-membered to 5-membered, which relieves considerable ring strain present in the cyclobutane ring (worth about 26 kcal/mol).

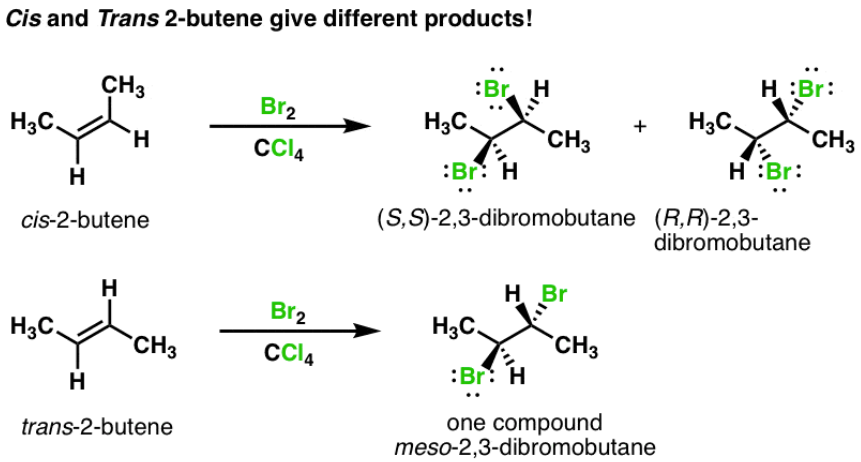
Bromination of alkenes



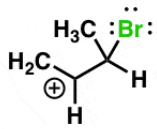
Rearrangements Are Never Observed



Stereospecific

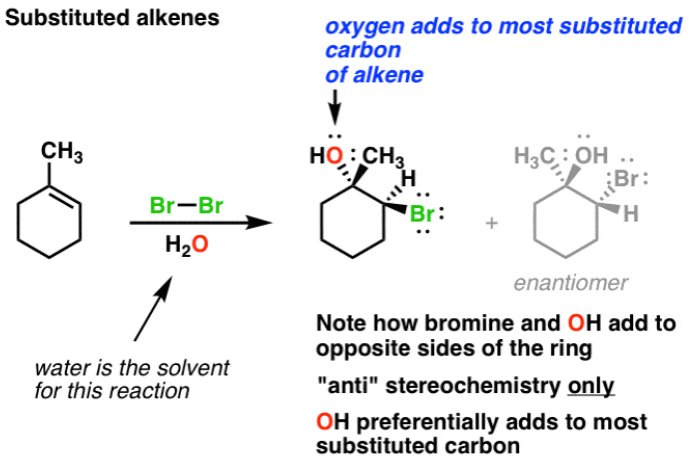


This is inconsistent with a carbocation intermediate



free rotation would allow for all possible 2,3-dibromobutane products from either isomer of 2-butene

Certain Solvents Can Affect The Reaction Products



What's even more interesting is that the reaction is regioselective. That is, when we have an unsymmetrical alkene, the major product is the one where water has added to the most substituted carbon of the alkene [most substituted = the sp2 carbon of the alkene directly attached to the fewest hydrogen atoms]. Such so-called "Markovnikov" selectivity was also observed in the reactions that proceed along the "carbocation pathway".