

Alkyl Halides

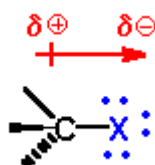
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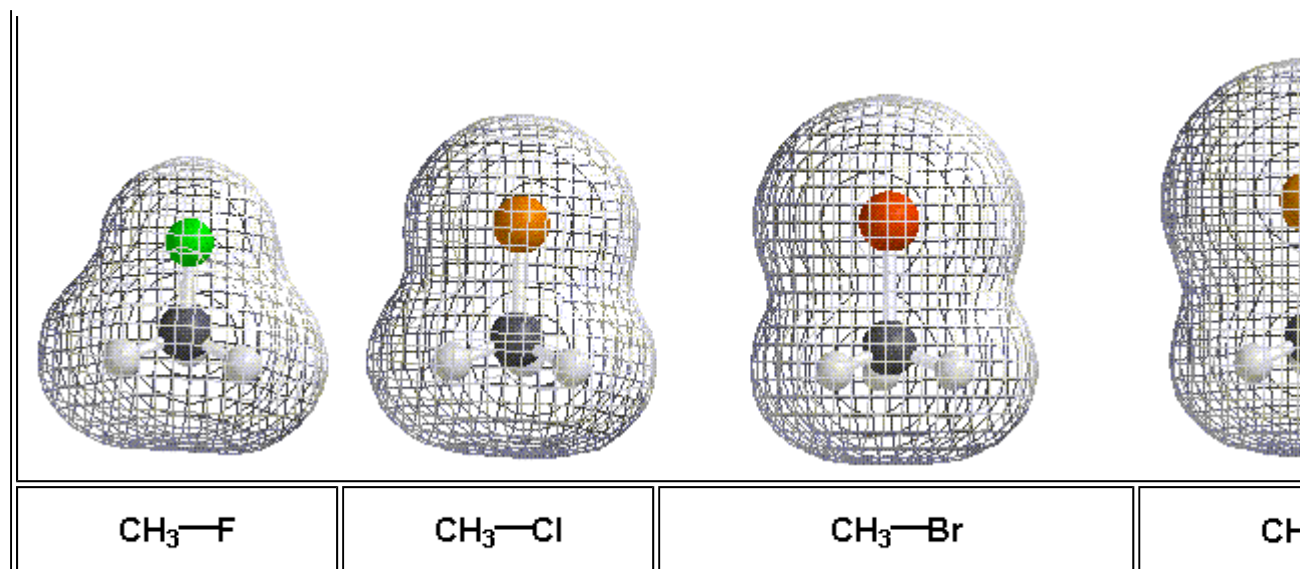
Structure

Organic halogen compounds are very common and important classes of organic molecules. Many organic halides occur in nature and others are produced in the laboratory. Thyroxine, a thyroid hormone, is an aryl iodide. Alkyl halides are nonflammable and nonpolar. These properties have made them useful as solvents for dry cleaning and degreasing applications. However, the toxicity of these compounds has led to substitutes for most of these applications. Even though chlorofluorocarbons are nonflammable, nontoxic and have mechanical properties that make them good refrigerants in air conditioners and refrigerators, the stability of these compounds in the troposphere and their ability to break down stratospheric ozone have led to a ban on these compounds. Chlorinated organic compounds have been widely used as pesticides. The discovery of the insecticidal properties of DDT in 1939 led to the development of the pesticide industries. The general anesthetic halothane is used instead of toxic agents like chloroform or flammable compounds like ether.

Because the halogens are more electronegative than carbon, the carbon-halogen bond is polarized. The carbon atom is partially positive and the halide is partially negative creating a dipole (charges separated by a distance).



Let's look at the electron density of the methyl halides. As we go to the larger halogens, the electron density increases because the valence electrons are located in shells farther from the nucleus.



Nomenclature for Alkyl Halides

IUPAC Rules

I. Identify the parent hydrocarbon

The longest continuous chain of carbon atoms containing the halogen atom is the parent.

II. Number the parent chain

Number the parent chain from the end nearest the halogen atom.

If the parent chain has branched alkyl groups, number the chain from the end nearest the first substituent, regardless if it is an alkyl group or halogen.

If the chain can be numbered from either end based on the position of the substituents, number from the end near the substituent that comes first alphabetically.

If a double or triple bond is present, it takes precedence over a halogen or alkyl substituent.

For cycloalkanes containing halogen substituents, begin numbering from the halogen atom unless a double or triple bond is present.

III. Assign each substituent a name and number

Name and number each substituent. Alkyl groups are named as described previously. Halogen atoms are named as **halo-** groups.

Names of Halogen Substituents		
halogen	substituent name	Symbol

fluorine	fluoro-	F
chlorine	chloro-	Cl
bromine	bromo-	Br
iodine	iodo-	I

If several of the same halogen atoms are present, use the prefixes di-, tri-, tetra-, etc.

List all substituents in alphabetical order.

Common Names

Simple alkyl halides are named in two parts. The first word is the name of the alkyl group and the second name is the name of the halogen.

Preparation of alkyl Halides

Bromination of Pentane

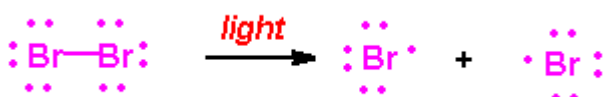
We have described alkanes as being relatively unreactive. This is true only for typical ionic reactions. Halogens react with alkanes very rapidly and highly exothermically in the presence of light or heat. If we prepare two test tubes containing pentane and bromine and mask one with black paper while the other is exposed to light from a slide projector, we see the effect of light on the reaction.



Click image to see a video of the bromination of pentane.

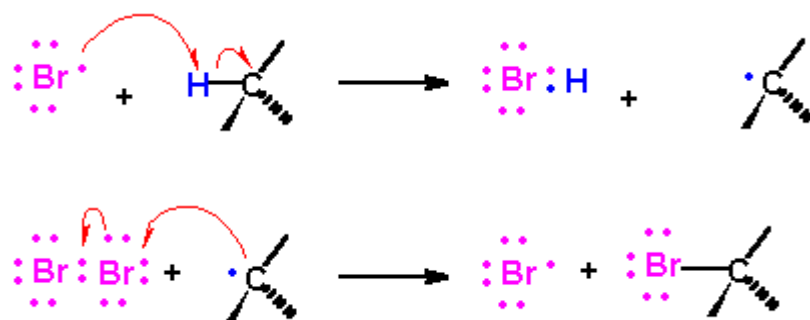
Why is light so important? A hint comes from the observation that bromine (like the other halogens chlorine and iodine) are colored. They absorb visible light. Light energy causes the diatomic halogen molecules to dissociate into atoms. Any species like halogen atoms which contain an unpaired electron are called free radicals. A process that forms a free radical from a species with paired electrons is called the initiation step of the free radical reaction. Heat can also be used to cleave halogen molecules into free radicals.

Initiation



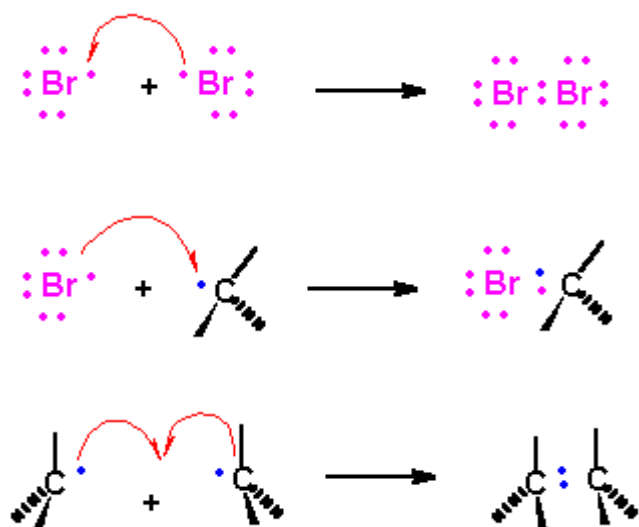
The bromine atoms are very reactive because of their unpaired electrons. They can react with each other and reform the bromine molecule, or they can react with pentane. A bromine atom reacts with pentane to remove (abstract) a hydrogen atom and form HBr and a carbon free radical. The carbon radical is also highly reactive and can react with a bromine molecule to produce an alkyl bromide and a new bromine radical. Reactions in which a molecule and a free radical react to form a new molecule and a new radical are called propagation steps.

Propagation



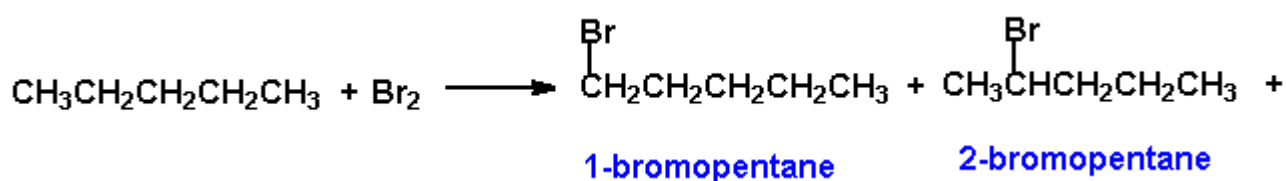
Because the bromine atom is a reactant in the first step and a product in the second step, this cycle of reactions can be repeated many times. The cycle stops when two radical species collide and form a nonradical molecule. These steps are termination steps.

Termination



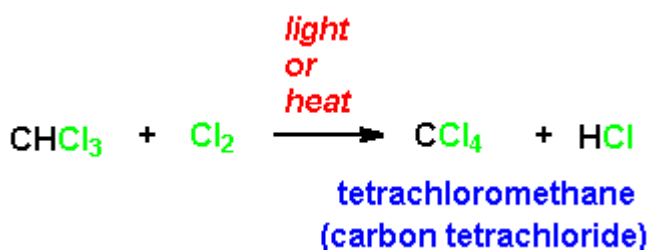
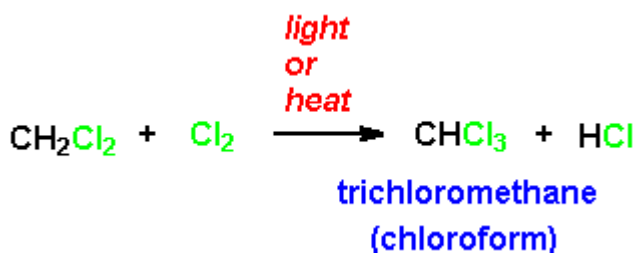
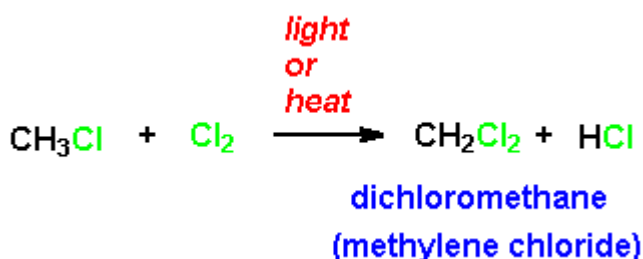
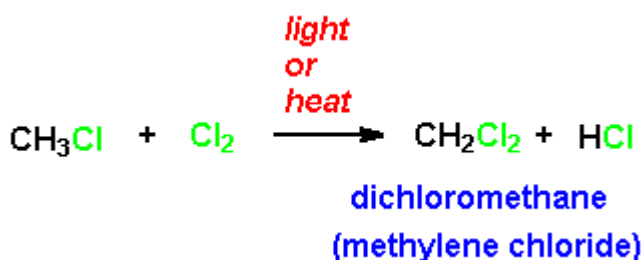
This mechanism accounts for the formation of the acid HBr in the reaction and bromopentane. A complication arises because pentane has three sets of hydrogen atoms that can be replaced with bromine to give the three straight chain bromopentane isomers.

Overall reaction



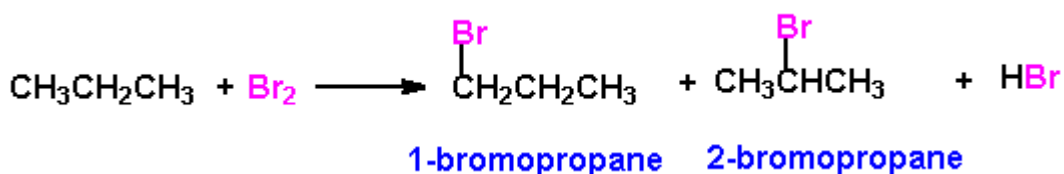
Free radical halogenation works well only for the halogens chlorine and bromine. The very high activation energy for abstraction of a hydrogen atom from a hydrocarbon by an iodine radical makes this process too slow. At the other extreme, the very low activation energy for abstraction of hydrogen by a fluorine radical and the highly exothermic nature of the reaction results in a violent, uncontrolled reaction.

Free radical reactions are not easily control. If the product of the reaction contains a C-H bond, it can react with a chlorine radical in another substitution reaction giving a polyhalogenated alkane. Chlorination of methane results in the initial formation of chloromethane. Chloromethane can react with chlorine to form dichloromethane (methylene chloride). Dichloromethane can react further to form trichloromethane (chloroform), and trichloromethane can react to form tetrachloromethane (carbon tetrachloride). All of these products are obtained in this reaction, and the products are separated by distillation.

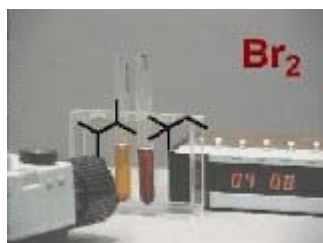


Regioselectivity of free-radical halogenation

Reaction of propane with bromine gives two monohalogenated products. Since one of several possible isomers predominates, the reaction is said to be regioselective.

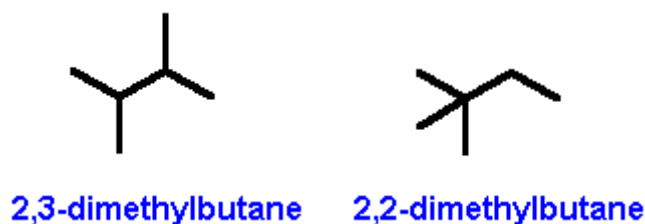


Why this difference in selectivity? Let's compare the rate of reaction of bromine with two isomeric hexanes - 2,3-dimethylbutane and 2,2-dimethylbutane.



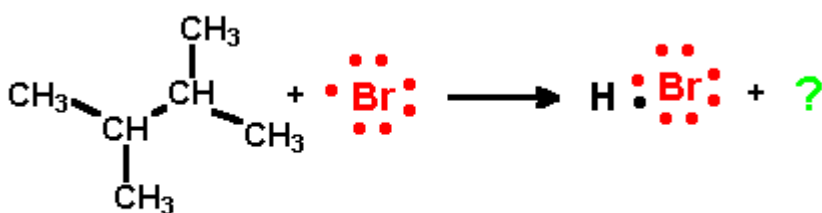
Bromination of 2,3-dimethyl butane and 2,2-dimethylbutane. Click on the image for a video of this reaction.

Which isomer reacts faster with bromine under free radical conditions?

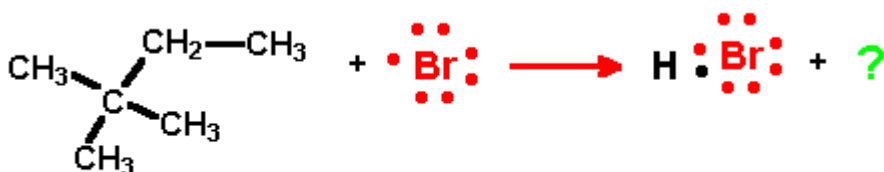


Click on the structure of the isomer which reacts faster with bromine in the presence of light.

Draw structures for the possible alkyl free radical intermediates that could be formed from each isomer by hydrogen abstraction by a bromine radical. Classify each radical species as 1°, 2°, or 3°. Compare your structures with those below.

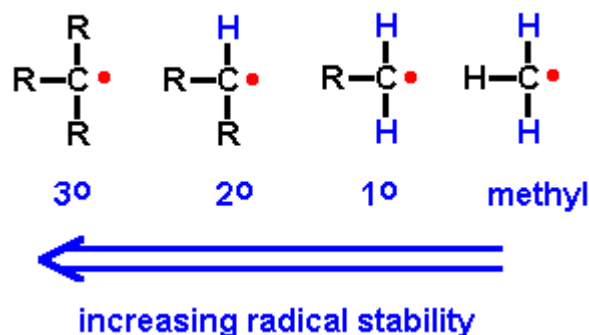


2,3-dimethylbutane



2,2-dimethylbutane

Free radicals are electron deficient species and their stability parallels that of carbocations - tertiary (3°) alkyl radicals are more stable than secondary (2°) alkyl radicals which are more stable than primary (1°) alkyl radicals.



Exercise: Observe the following experiment determining the relative rate of reaction of alkyl benzenes - methyl benzene, ethyl benzene, and isopropyl benzene.

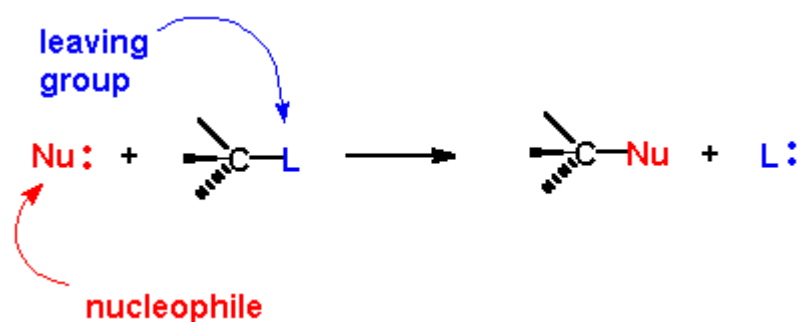


Click image to see a video of the bromination of alkyl benzenes

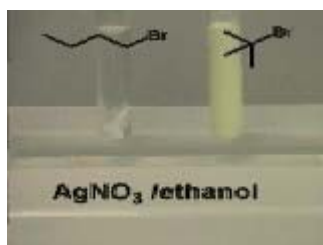
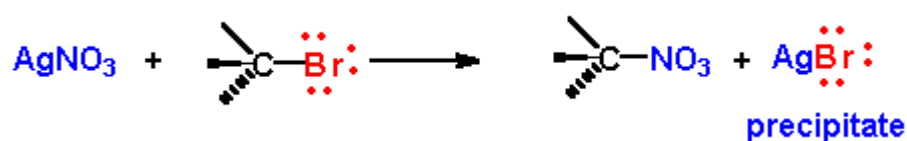
- [What is the relative order of reactivity?](#)
- [Does this order reflect the stability of the free radical intermediates for the different alkyl benzenes?](#)

Nucleophilic Substitution

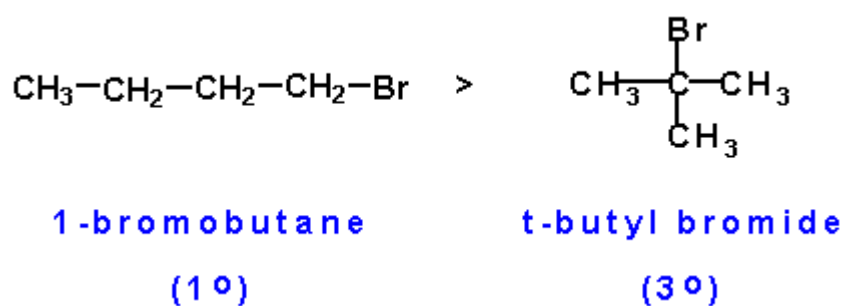
The polarization of the carbon-halogen bond makes it a reactive site in organic molecules. A very common reaction of alkyl halides is nucleophilic substitution. A nucleophile can donate a pair of electrons to the electrophilic carbon atom of the alkyl halide forming a new bond and displacing the halide. In general terms, any electronegative group displaced by a nucleophile is called a leaving group. Halides are very common and important leaving groups in organic chemistry.



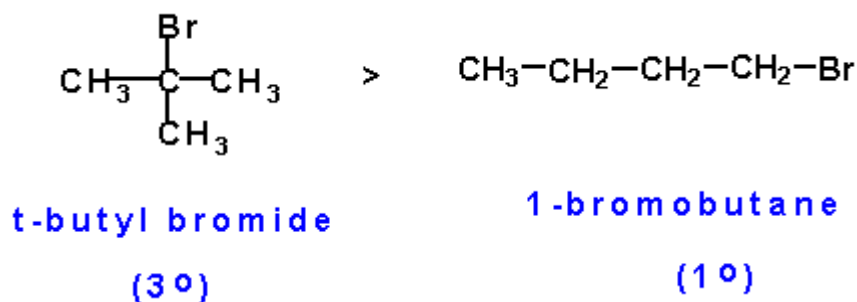
Let's look at the substitution of two bromobutane isomers with silver nitrate in ethanol. The reaction produces insoluble silver bromide.



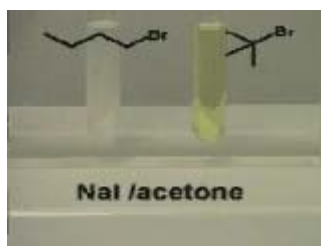
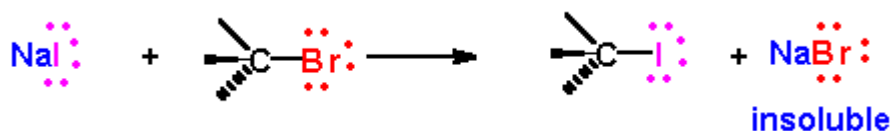
Which order of reactivity is observed in this reaction?



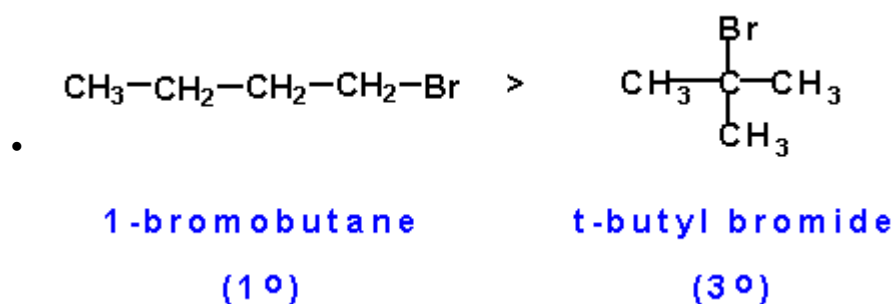
or



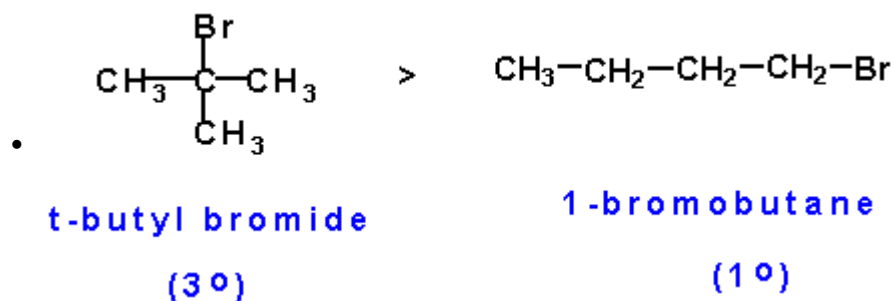
Let's look at the reaction of these same alkyl halides under different reaction conditions. This time we will add the alkyl halides to a solution of sodium iodide in acetone. We can monitor the progress of the reaction by the formation of a precipitate of sodium bromide.



Which order of reactivity is observed in this reaction?



or



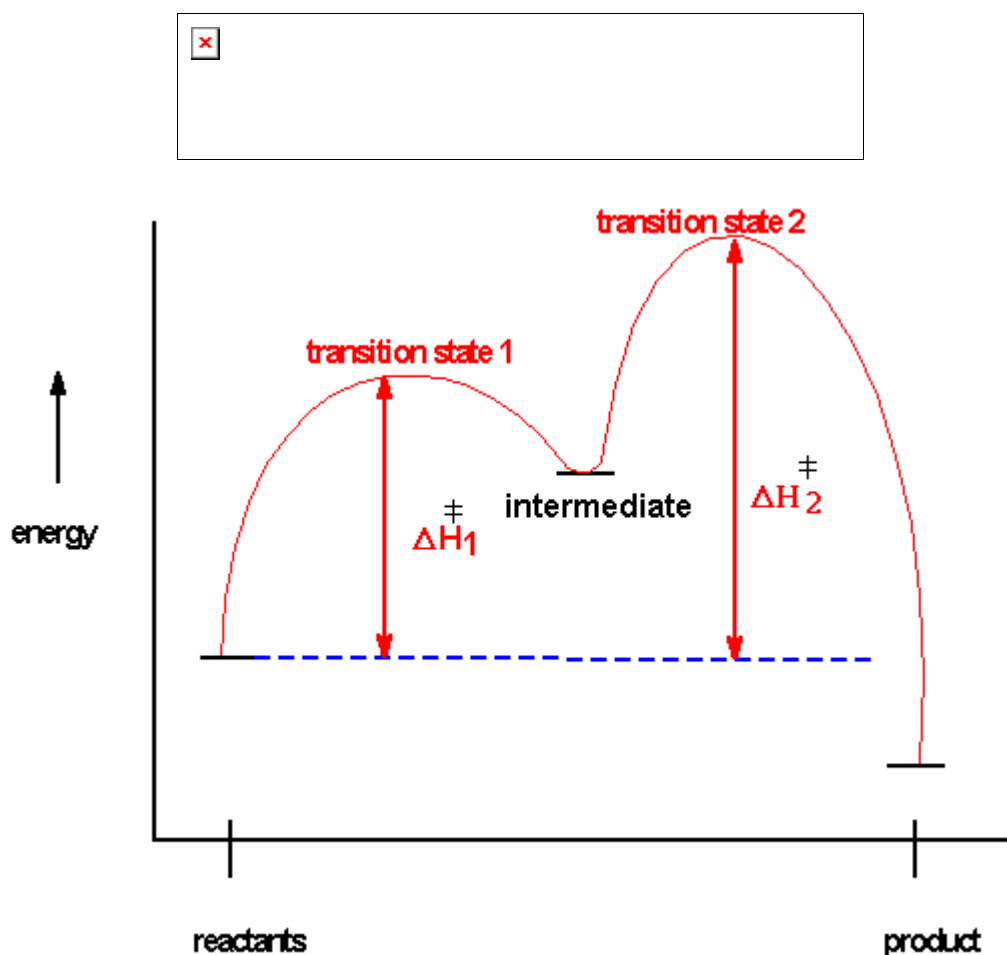
Why does the order of reactivity of a series of isomers change under different reaction conditions? The answer must lie in a difference in mechanism of the two reactions. Organic chemists study reactions by asking a variety of questions.

- What are the products of the reaction?
- How do the conditions of the reaction affect the product?
- What factors affect the rate of the reaction?
- What intermediates, if any, are formed?
- What is the stereochemistry of the reactants and products?

Based on these considerations, nucleophilic substitution reactions are classified by one of two reaction mechanisms - $\text{S}_{\text{N}}1$ (Substitution, Nucleophilic, unimolecular) or $\text{S}_{\text{N}}2$ (Substitution, Nucleophilic, bimolecular).

The terms unimolecular and bimolecular describe the kinetics of the reaction. Chemical reactions can

involve a number of steps between the reactants and the products. The overall rate of the reaction is determined by the slowest step of the reaction. This is reasonable when you look at the energy diagram for a hypothetical reaction involving two steps (one in which there is an intermediate between the reactants and products). The rate of the reaction is determined by the highest energy transition state. This is the bottleneck of the reaction. The process that leads directly to this highest energy transition state is the rate-determining step of the reaction. Consider the following reaction. The first step is faster (lower energy transition state) than the second step. The overall rate of the reaction is controlled by the second step of the reaction (rate determining step). If only one species is involved in the rate-determining step, the reaction is unimolecular. If two species are involved in the rate-determining step, the reaction is bimolecular.

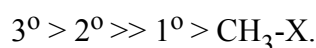


S_N1 Mechanism

The solvolysis of the butyl bromides in water takes place by an S_N1 mechanism. The 1 indicates that the reaction is unimolecular - only one species is involved in the slow step of the reaction. The rate depends only on the concentration of the alkyl halide, not the nucleophile.

Order of Reactivity

The order of reactivity for an S_N1 reaction is:



Observe that this order of reactivity parallels the stability of carbocations. It is reasonable to suggest

that the S_N1 reaction involves two steps:

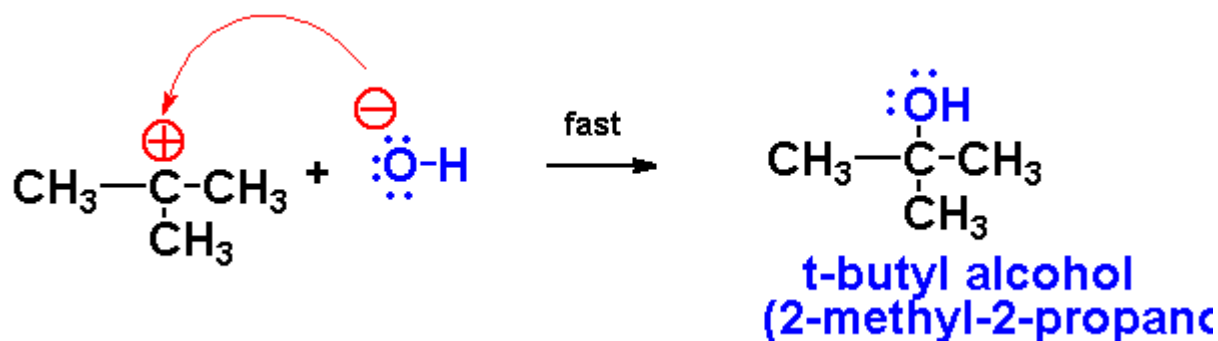
- slow (rate determining) step - ionization of the alkyl halide to form a carbocation
- fast step - addition of the nucleophile to the carbocation

For the solvolysis of t-butyl bromide in water containing some sodium hydroxide:

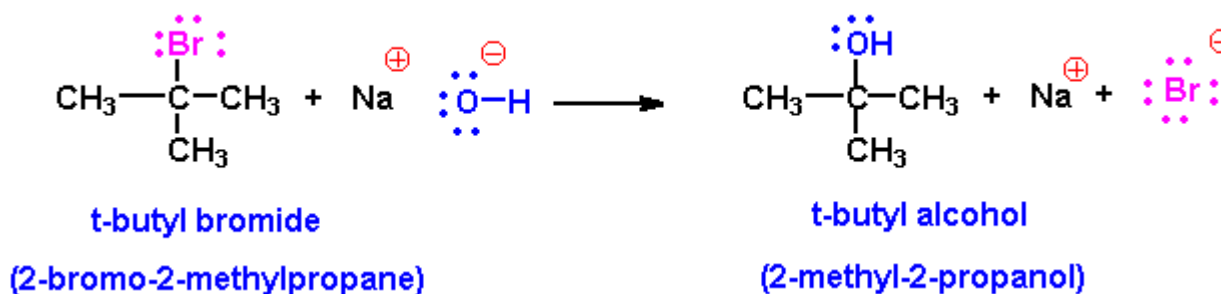


t-butyl bromide
(2-bromo-2-methylpropane)

- fast step:

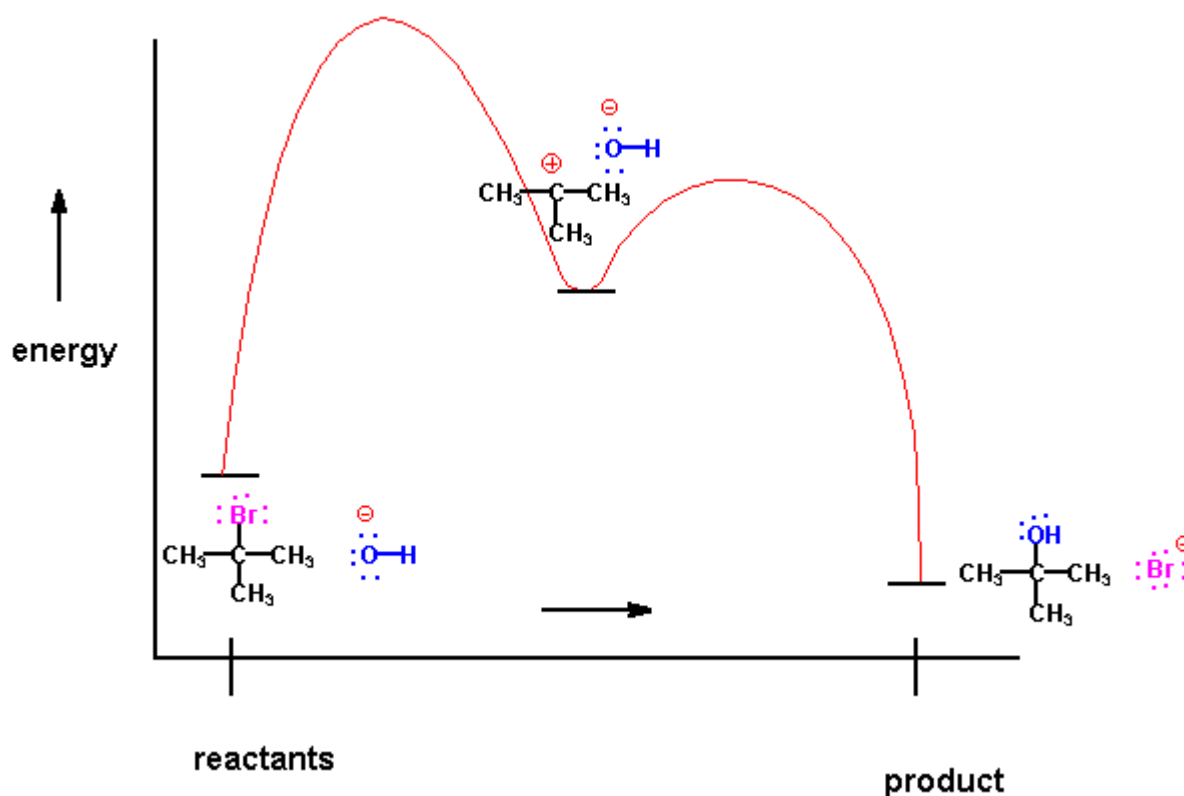


- net reaction



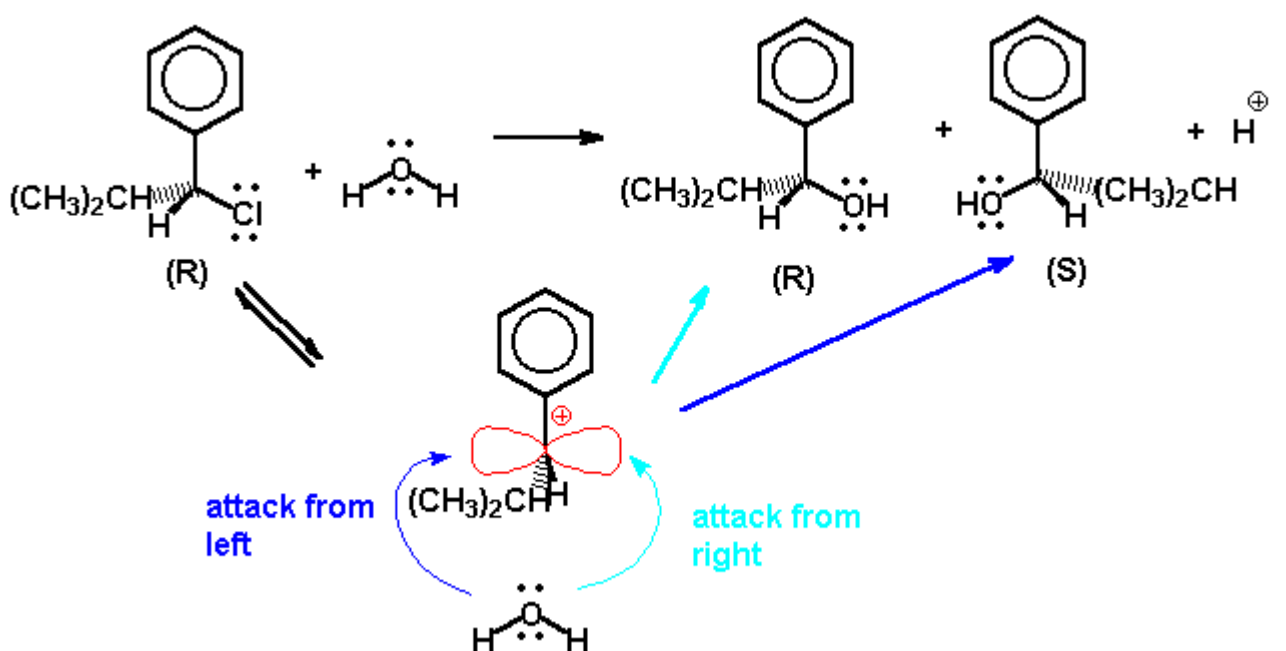
Click here to see an [animation](#) of the S_N1 mechanism.

This sequence of reactions can be represented on an energy diagram. Note that the formation of the carbocation is the high energy (slow) step. Addition of the nucleophile to the carbocation is very rapid.



Stereochemistry

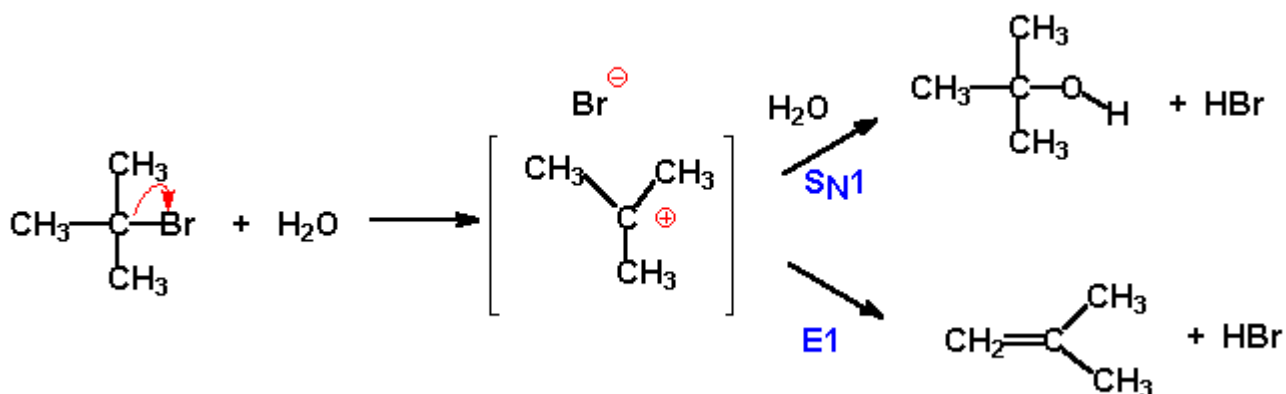
If the above mechanism for an S_N1 mechanism is correct, the intermediate sp^2 carbocation should be planar. The nucleophile should add equally well from either side of the plane. As a consequence, a S_N1 reaction at a chiral carbon will give a mixture of both enantiomers arising from both retention and inversion of configuration at the chiral center (racemization). For example, (R)-1-chloro-1-phenylbutane undergoes solvolysis in water to give an optically inactive product - a racemic mixture of the enantiomeric alcohols. Click here for an [animation](#) of this process.



E1 (Elimination reaction)

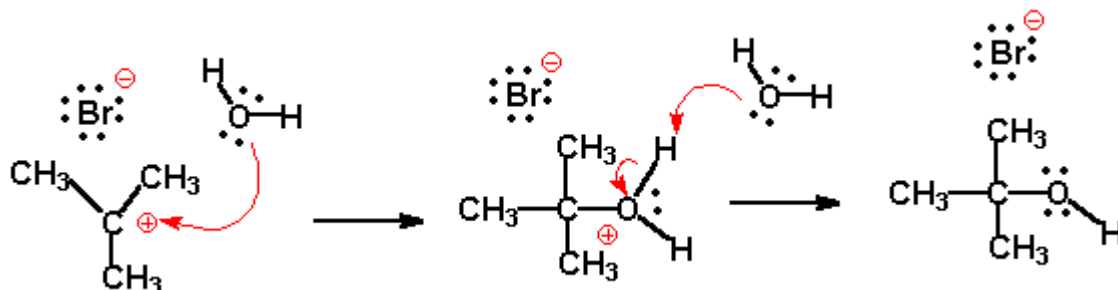
A carbocation is formed in the slow step of an S_N1 reaction. If a nucleophile attacks the carbocation, a substitution reaction occurs. Alternatively, a base can abstract a hydrogen atom from a carbon atom adjacent to the carbocation forming a double bond. This process is called an elimination reaction and since this mechanism involves only one species in the rate determining step, it is called an $E1$ reaction. We have seen an example of this reaction in the preparation of alkenes by dehydration of alcohols.

Because they involve a common intermediate, the $E1$ and S_N1 reactions compete with each other. Consider the solvolysis of *t*-butyl bromide in water.



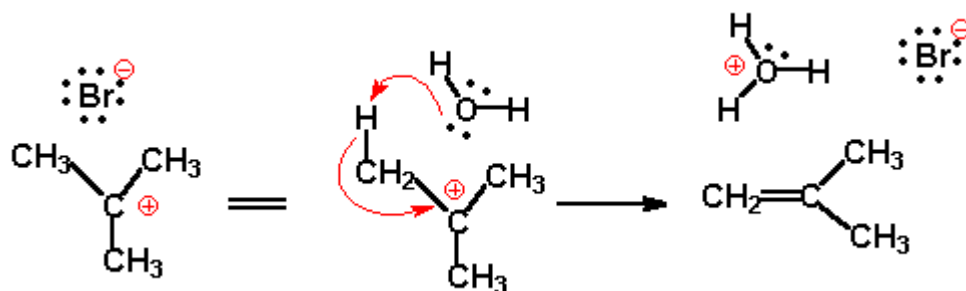
The overall reaction involves the following steps:

- Ionization of alkyl halide to form a carbocation.
 - Attack of a nucleophile on the carbocation (S_N1).



or

- Attack of a base on a H atom on a carbon atom adjacent to the carbocation ($E1$).

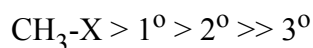


S_N2 Mechanism

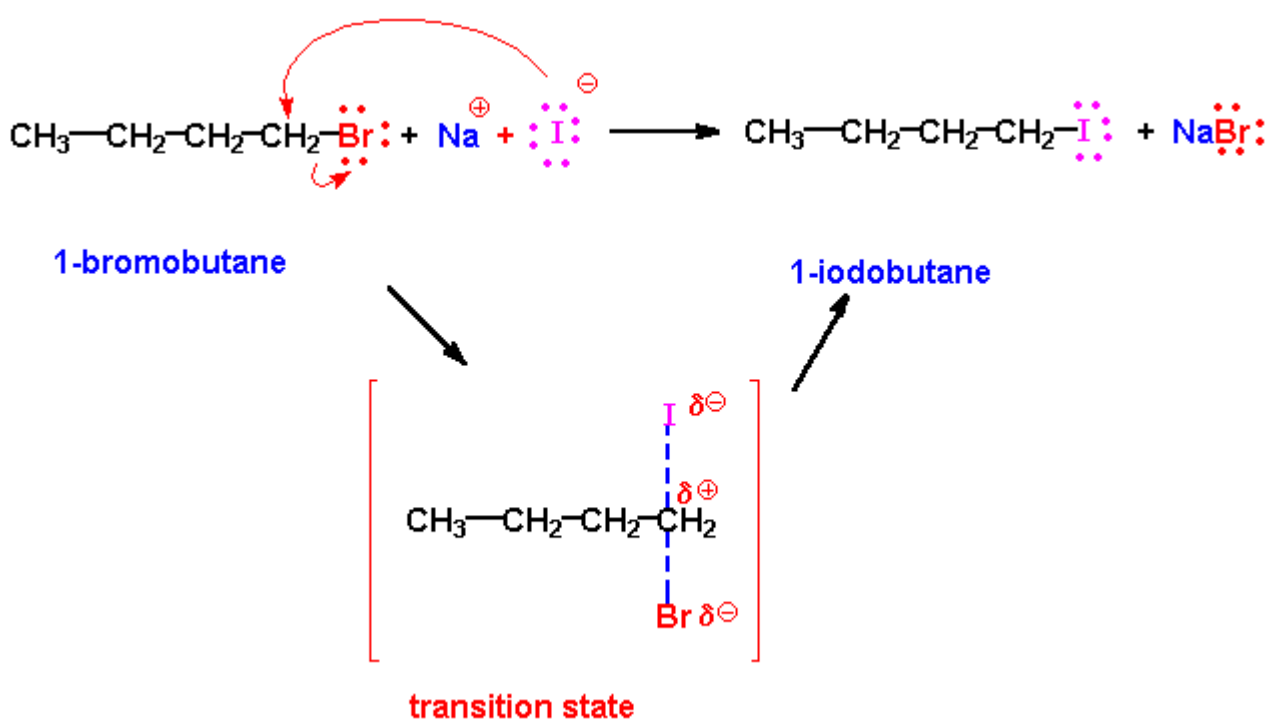
The reaction of the butyl bromides with iodide in acetone takes place by an S_N2 mechanism. The 2 indicates that the reaction is bimolecular - two species are involved in the slow step of the reaction. The rate depends on the concentration of both the alkyl halide and the iodide ion (nucleophile.).

Order of Reactivity

The order of reactivity for an S_N2 reaction is:

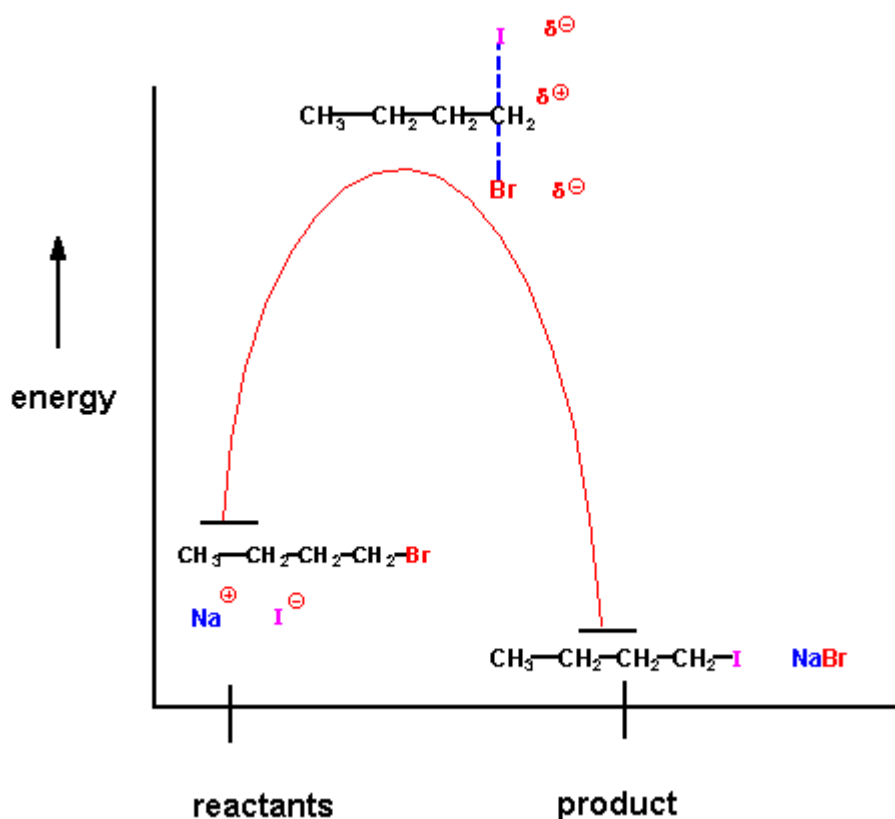


An S_N2 reaction takes place in one step - attack of the nucleophile on the alkyl halide. This reaction does not have an intermediate. A transition state is formed in which the bond between the nucleophile and carbon atom is being formed at the same time the bond between the carbon atom and the leaving group is being broken. Reactions in which bond forming and bond breaking occur at the same time are called concerted reactions.



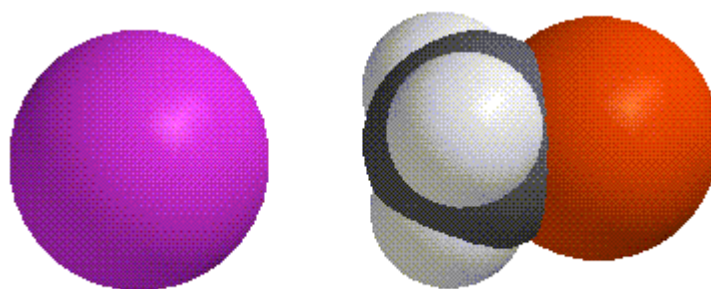
Click here for an [animation](#) of the S_N2 process.

The energy diagram for the S_N2 reaction reveals the one-step process.

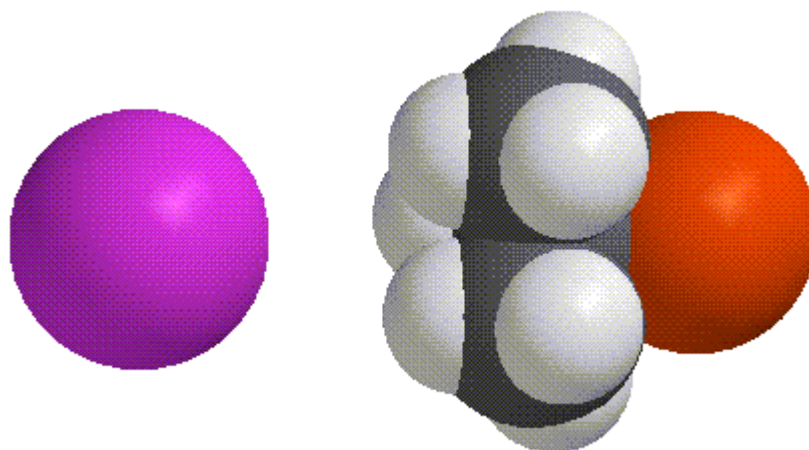


Stereochemistry

In an S_N2 reaction the nucleophile must approach the carbon atom bearing the leaving group to begin to form a bond. This requirement makes the reaction very sensitive to steric factors. Compare the reaction of an iodide ion with methyl bromide and t-butyl bromide.



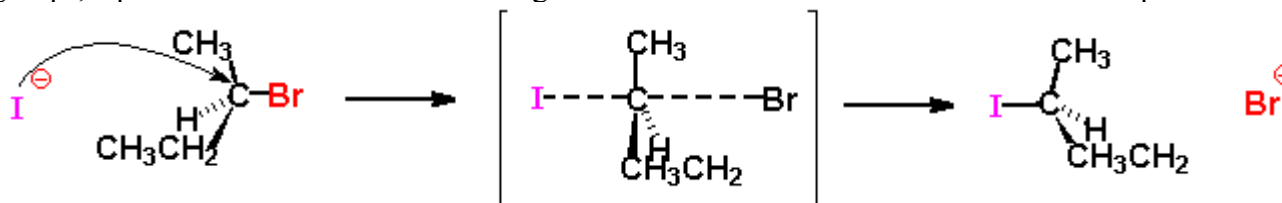
Reaction of iodide ion with methyl bromide. The small size of the hydrogen atoms allow the iodide ion to approach the carbon atom within bonding distance.



Reaction of iodide ion with t-butyl bromide. The bulky methyl groups block the approach of the iodide ion to the carbon atom.

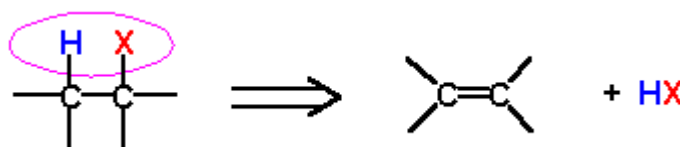
Steric hindrance to backside attack of the nucleophile is most significant in tertiary halides and decreases as alkyl groups are replaced by hydrogen atoms. This explains the order of reactivity for S_N2 reactions. Steric hindrance also applies to the nucleophile. Very hindered nucleophiles are less reactive than smaller nucleophiles. For example, t-butoxide is less nucleophilic than methoxide.

Backside displacement of the leaving group by the nucleophile accounts for the observation that reaction of a nucleophile at a chiral center leads to a product with the opposite arrangement of groups, a process called inversion of configuration. Click here to see an [animation](#) of this process.



Elimination Reactions

Elimination reactions most commonly occur when a hydrogen atom on one carbon atom and a leaving group on an adjacent carbon are removed forming a double bond.

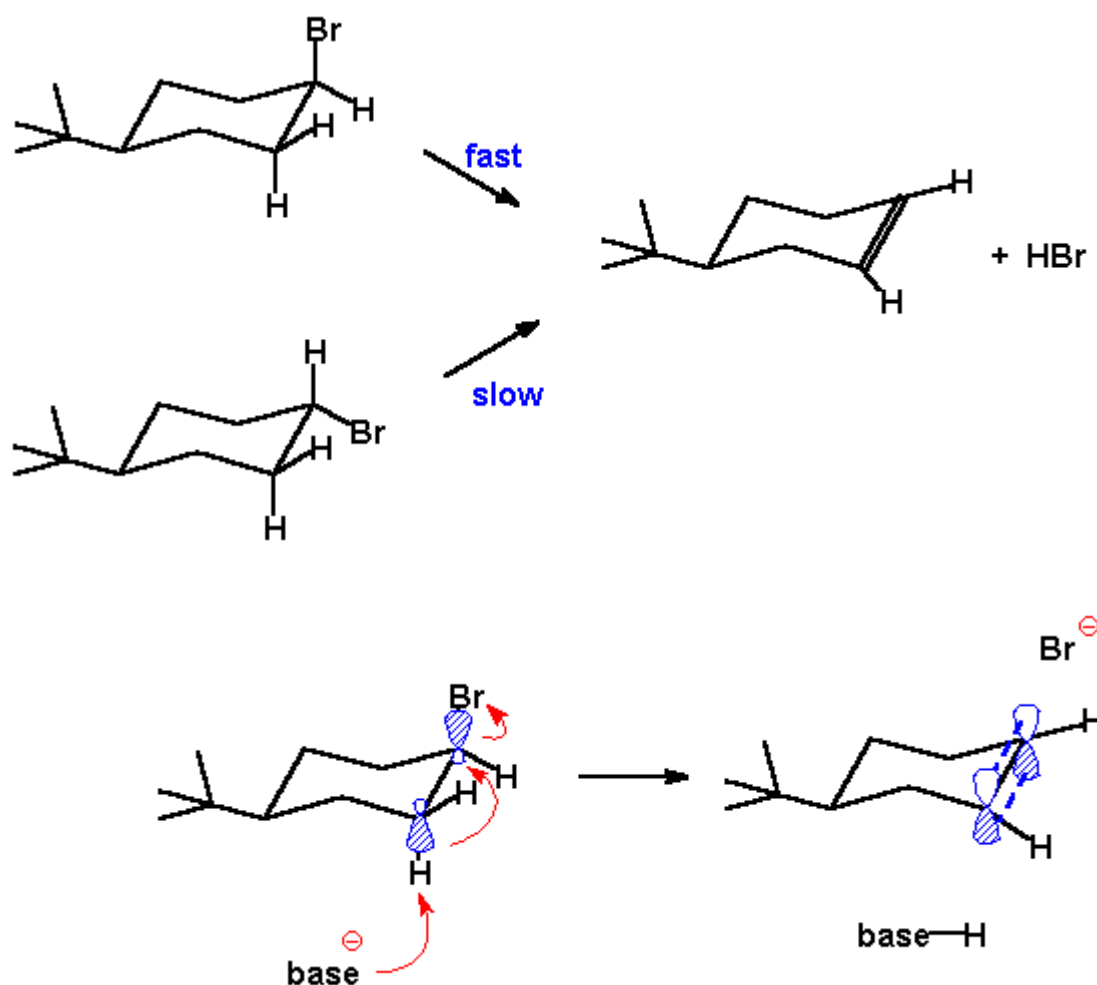


Elimination reactions, like nucleophilic substitution reactions, can be either unimolecular (E1) or bimolecular (E2) processes. We have seen that the E1 process competes with the S_N1 reaction through a common carbocation intermediate. The E1 process is favored with alkyl halides that form stable carbocations (resonance stabilized carbocations or tertiary halides). The E2 process involves

both the alkyl halide and a base in the rate determining step and is favored when strong bases are present.

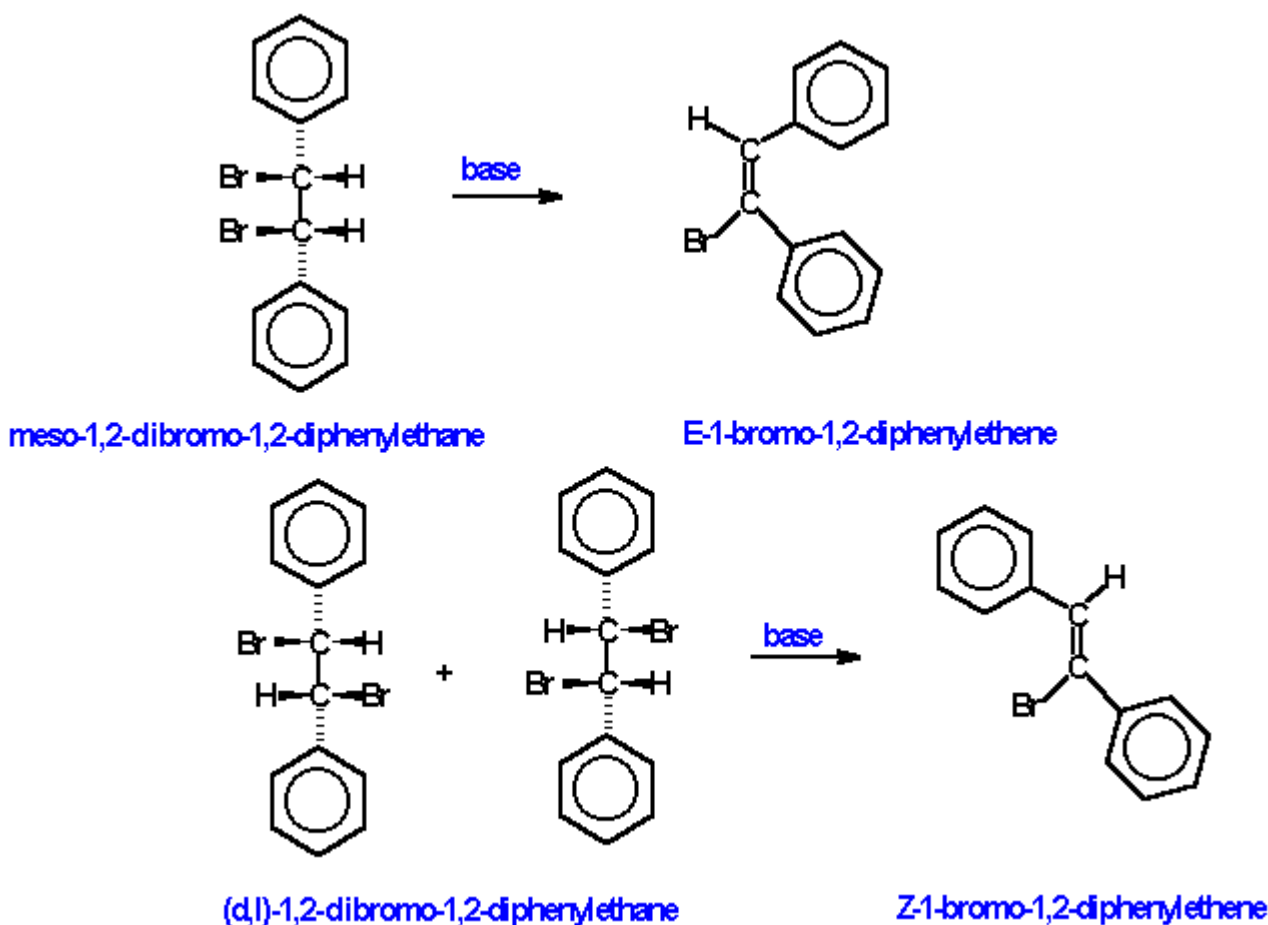
E2

Since the E2 reaction is bimolecular, both the bond forming and bond breaking processes have to occur at the same time (a concerted process). For this to happen the orbitals of the C-H and C-X bonds being broken must be properly aligned so that the pi bond is formed. A good example is observed in the base catalyzed elimination of 4-bromo-1,1-dimethylcyclohexane. The isomer with an axial bromine undergoes elimination much faster than the one with the equatorial bromine. The mechanism proposed for this reaction involves a transition state in which the C-H and C-X bonds are in an arrangement described as anti-periplanar.

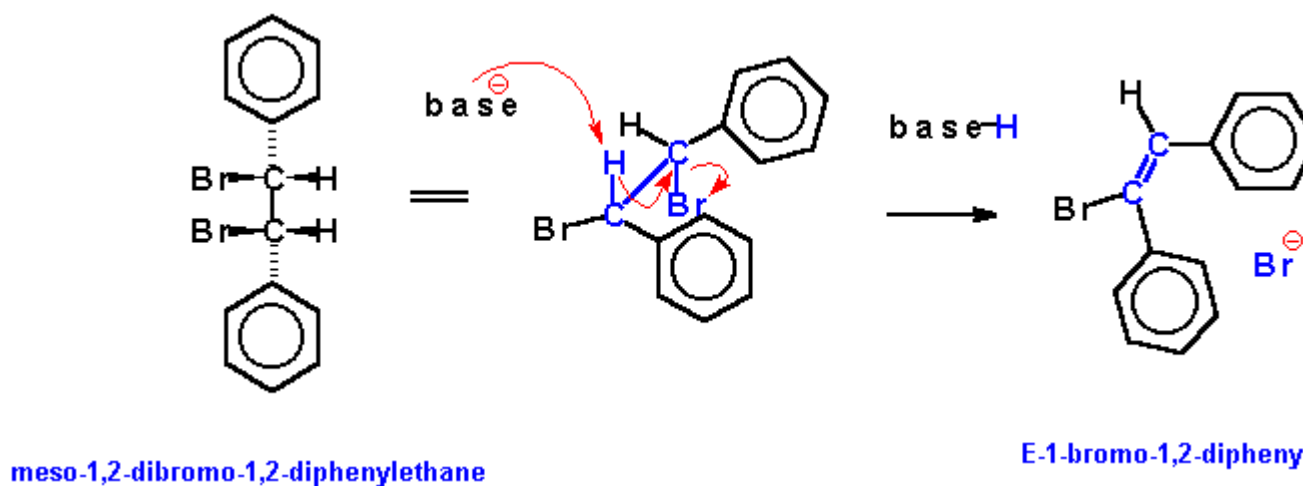


Anti-periplanar arrangement of orbitals in transition state of an E2 reaction.

The requirement for an anti-periplanar arrangement of bonds makes the E2 reaction stereospecific (a reaction in which only one stereoisomer is formed). A classic example is the elimination of 1,2-dibromo-1,2-diphenylethane. The meso- diastereomer undergoes elimination to form E-1-bromo-1,2-diphenylethene while elimination of the d,l- diastereomers gives the Z-alkene.



These observations can be explained by orienting the molecule in the anti-periplanar arrangement. For the meso-diastereomer, rotation about the C-C single bonds gives the proper orientation for elimination. This arrangement places the two phenyl groups adjacent to each other.



Exercise: Show that E2 elimination of the d,l-enantiomers produces Z-1-bromo-1,2-diphenylethene.

Structure of the Product

Both E1 and E2 eliminations generally favor the more stable (more highly substituted) alkene when several possible products may be formed. This is often referred to as a Saytzeff elimination.

Summary of Nucleophilic Substitution and Elimination Reactions

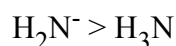
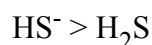
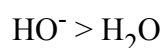
Factors affecting nucleophilic substitution reactions

Nature of the nucleophile

Nucleophiles possess an unshared electron pair and replace a leaving group. Substances which can donate a pair of electrons can also act as bases in elimination reactions. Thus, nucleophilic substitution always competes with elimination. Nucleophilicity (a measure of the ability of a substance to bind to an electrophilic carbon atom) and basicity (a measure of the ability of a substance to bind to a proton) are not the same. In general strong bases are good nucleophiles, but there is not a direct correlation between base strength and nucleophilicity. Several factors allow prediction of relative nucleophilicity of a potential nucleophile, and thus, the course of a reaction.

- Charge

Anions are more nucleophilic (and basic) than their neutral counterparts. Thus:



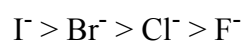
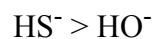
- Trends within a period

Both of these properties are affected by electronegativity and polarizability of the atoms involved. Electronegativity is the attraction of an atom for electrons. For atoms with the same valence shell (in the same row of the periodic table) and having the same charge, the elements to the right in the periodic table are less nucleophilic. For the second row elements, nucleophilicity decreases as we go from left to right in the periodic table. This is also the trend for basicity.



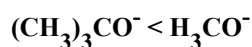
- Trends within a group

As we go down a group in the periodic table, the size of the atom or ion increases because we are adding more electron shells. These outer shells far from the nucleus are easily distorted by nearby charged or partially charged atoms, a property called polarizability. The sulfide ion is more nucleophilic than the hydroxide ion even though it is a weaker base. The same trend is seen for the halide ions.



- Steric Effects

We have seen that the S_N2 reaction requires the nucleophile to approach a tetrahedral carbon atom to within bonding distance. For bulky nucleophiles, this approach is more difficult. Common examples are seen in the relative nucleophilicities of alkoxide ions.



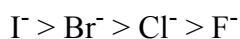
Nature of the solvent

The solvent can determine whether a reaction occurs by a substitution or elimination pathway. In general, polar solvents stabilize polar and charged species and favor reactions involving carbocation (S_N1 and $E1$ reactions). Common polar solvents are water, methanol, ethanol, acetic acid, dimethyl sulfoxide, and dimethylformamide.

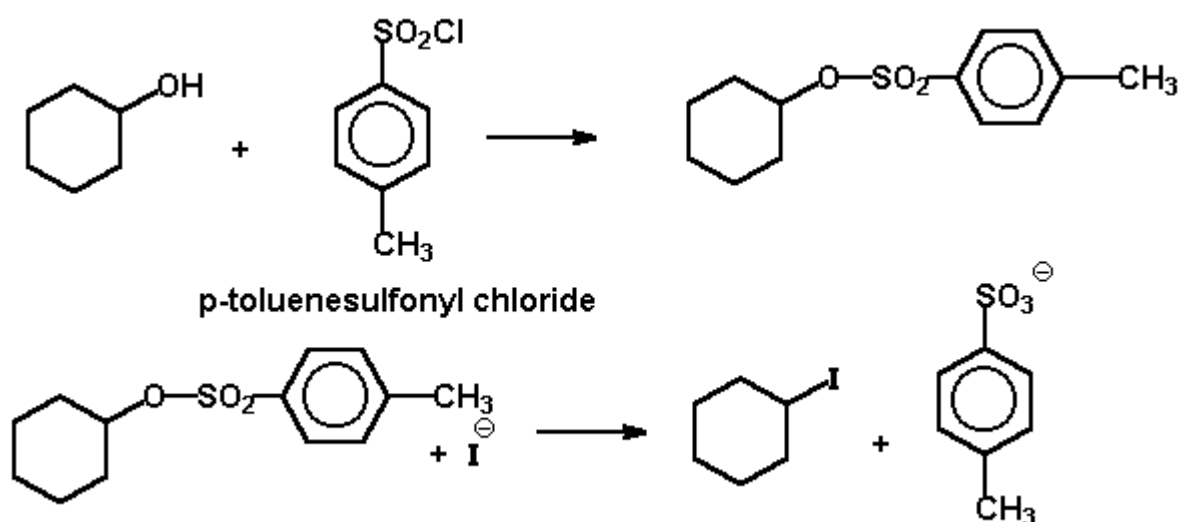
Nature of the leaving group

Neutral molecules are better leaving groups than their conjugated bases. Thus, water is a good leaving group and hydroxide is a very poor leaving group. We have seen that elimination reactions of alcohols require an acid catalyst to protonate the OH group so that H_2O is eliminated.

Halide ions are very common leaving groups. In general, the best leaving groups are the weakest bases. Thus:



A very important leaving group in organic chemistry is p-toluenesulfonate (tosyl) group. This group is often used to convert alcohols into good leaving groups without requiring strongly acidic reaction conditions. In biochemical systems, phosphate esters are very common leaving groups and serve the same purpose of making OH groups into good leaving groups.



Structure of the substrate

We have seen that the relative rates of substitution and elimination reactions are greatly influenced by the structure of the alkyl halide.

S_N1 and E1	$3^\circ > 2^\circ \gg 1^\circ > \text{CH}_3\text{-X}$
S_N2	$\text{CH}_3\text{-X} > 1^\circ > 2^\circ \gg 3^\circ$

Summary

In predicting whether an alkyl halide will undergo substitution or elimination, the following generalizations can be made:

Factors favoring Substitution or Elimination Reactions				
(Black boxes indicate that the reaction mechanism is not possible for that halide)				
Halide	S_N1	S_N2	E1	E2
1°		<ul style="list-style-type: none"> • most conditions 		<ul style="list-style-type: none"> • strong bases
2°	<ul style="list-style-type: none"> • polar solvents 	<ul style="list-style-type: none"> • nonpolar solvents • good nucleophiles 	<ul style="list-style-type: none"> • polar solvents • poor nucleophiles 	<ul style="list-style-type: none"> • strong bases
3°	<ul style="list-style-type: none"> • polar solvents • nonbasic nucleophiles 		<ul style="list-style-type: none"> • polar solvents • poor nucleophiles 	<ul style="list-style-type: none"> • strong bases