Organic Reactions & Reaction Mechanisms

Organic reactions are chemical reactions involving organic compounds. The basic organic chemistry reaction types are addition reactions, elimination reactions, substitution reactions, pericyclic reactions, rearrangement reactions, photochemical reactions, and redox reactions. In organic synthesis, organic reactions are used in the construction of new organic molecules.

1. Addition Reactions:

* Electrophilic Addition ----Includes such reactions as halogenation, hydrohalogenation, and hydration.

* Nucleophilic Addition

* Radical Addition

2. Elimination Reaction: Include processes such as dehydration and are found to follow an E1, E2, or E1cB reaction mechanism.

3. Substitution Reactions:

Nucleophilic Aliphatic Substitution with SN1, SN2, and SNi reaction mechanisms.

*Nucleophilic Aromatic Substitution

* Nucleophilic Acyl Substitution

* Electrophilic Substitution

* Electrophilic Aromatic Substitution

* Radical Substitution

4. Rearrangement Reactions:

* 1,2-Rearrangements

* Pericyclic Reactions

* Metathesis

* ADDITION REACTIONS

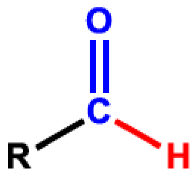
- Addition Reactions reaction is in which atoms or groups of atoms are simply added to a double bond without the elimination of atoms or other molecules.

Conceptually, additional reactions follow the opposite pathway of β – elimination reactions and they are categorized into two classes; ionic reactions which involve an ionic intermediate, and non-ionic reactions which do not involve ionic intermediates. Ionic reactions are further subdivided into two types: nucleophilic additions and electrophilic additions. Similarly, non-ionic reactions comprise free radical additions and concerted additions.

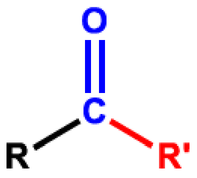
Nucleophilic Addition Reactions:

Nucleophilic Addition Reactions to Aldehydes and Ketones

Aldehydes and ketones are organic compounds that possess a carbonyl group attached to a hydrogen atom in the case of aldehyde, and an alkyl or aryl group in the case of ketones. The main reaction of these compounds is nucleophilic addition whereby a nucleophile adds to the carbonyl carbon atom while the oxygen receives a hydrogen proton.

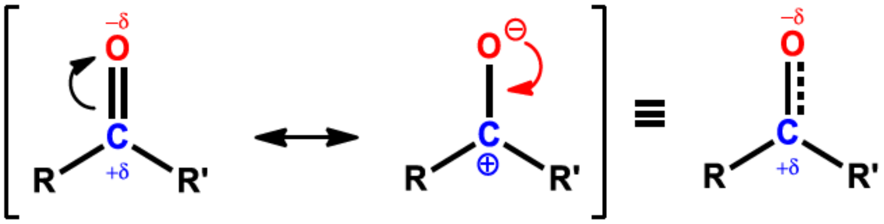


Aldehydes



Ketones

Since oxygen is more electronegative than carbon atoms, it pulls the electron of the carbonyl double bonds toward its nucleus. As a result, a partial negative charge forms on the oxygen atom while a partial positive charge forms on carbonyl carbon. This particular property makes aldehyde and ketones suitable for nucleophilic addition reactions.



Reactivity of Aldehydes and Ketones

In terms of reactivity towards nucleophiles, aldehydes are more reactive than ketones due to the steric strain in ketones, which makes the electrophilic site less accessible.

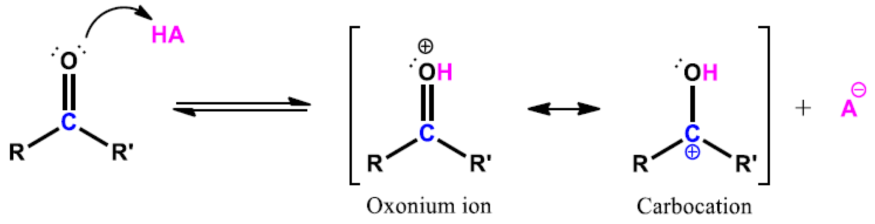
On the other hand, ketones tend to be more stable than aldehydes since the carbonyl group in ketones is attached to two electron-releasing groups that can be alkyl +*I* or aryls +*M*.

General Mechanism

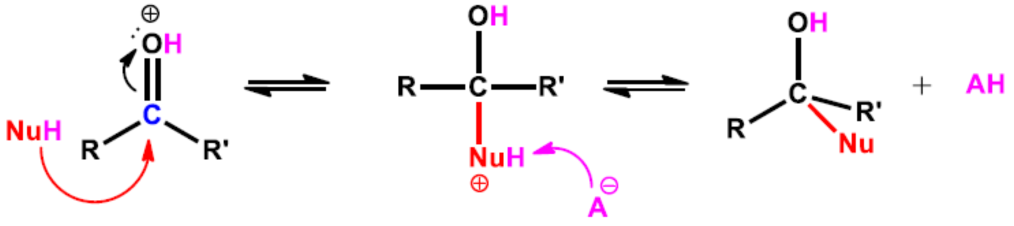
Nucleophile addition to aldehydes and ketones can be carried out with acid or base catalyst and it proceeds in two steps.

Acid-Catalyzed Reactions

Under acidic conditions, the first step consists in protonating the carbonyl oxygen, which gives rise to a more electrophilic carbonyl carbon.

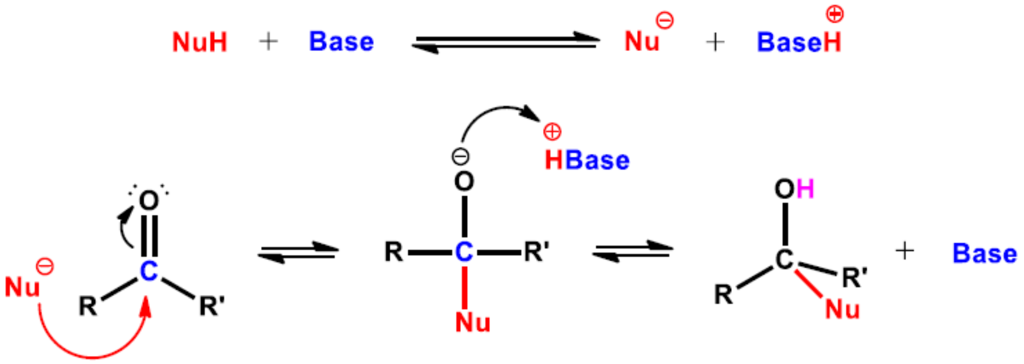


In the next step, the nucleophile adds to the carbonyl carbon atom resulting in an ionic tetrahedral intermediate, which then gets deprotonated to form a hydroxy group.

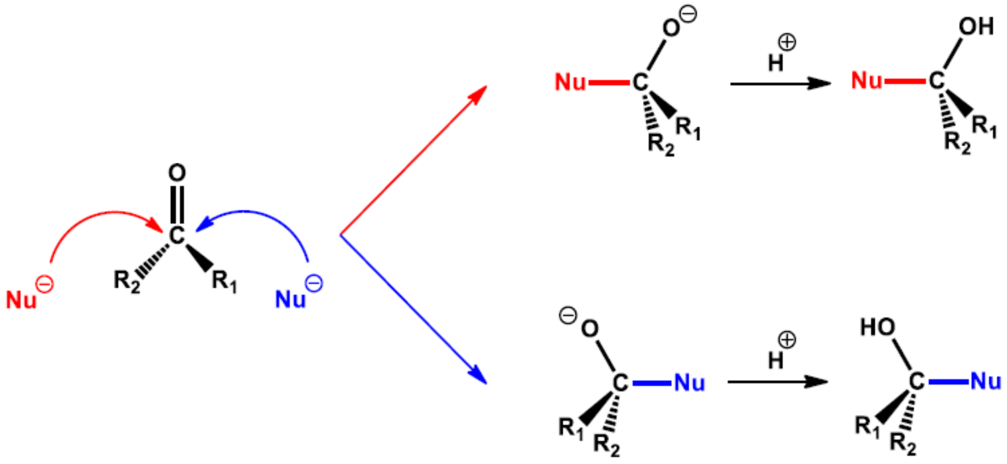


Base Catalyzed Reactions

When performing a nucleophilic addition reaction under basic conditions, the nucleophile first reacts with the base to generate a stronger nucleophile, which then adds to the carbonyl carbon resulting in an ionic tetrahedral intermediate. The next step involves the protonation of the ionic intermediate, which can be accomplished by either a protic solvent or the conjugate acid of the base catalyst.



Carbonyl carbon is a sp2 hybridized carbon that has a planar geometry. As a result, during nucleophilic addition, the nucleophile can add from either side of the carbonyl carbon resulting in a mixture of two stereoisomers, which makes nucleophilic addition a **non-stereoselective** reaction.

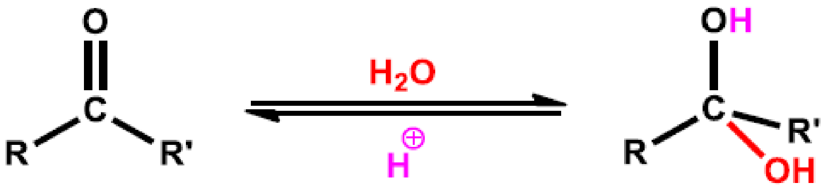


Common Reactions of Aldehydes and Ketones

Nucleophilic addition to aldehydes and ketones is a fundamental reaction in organic chemistry since it transforms carbonyl function into other reactive functional groups.

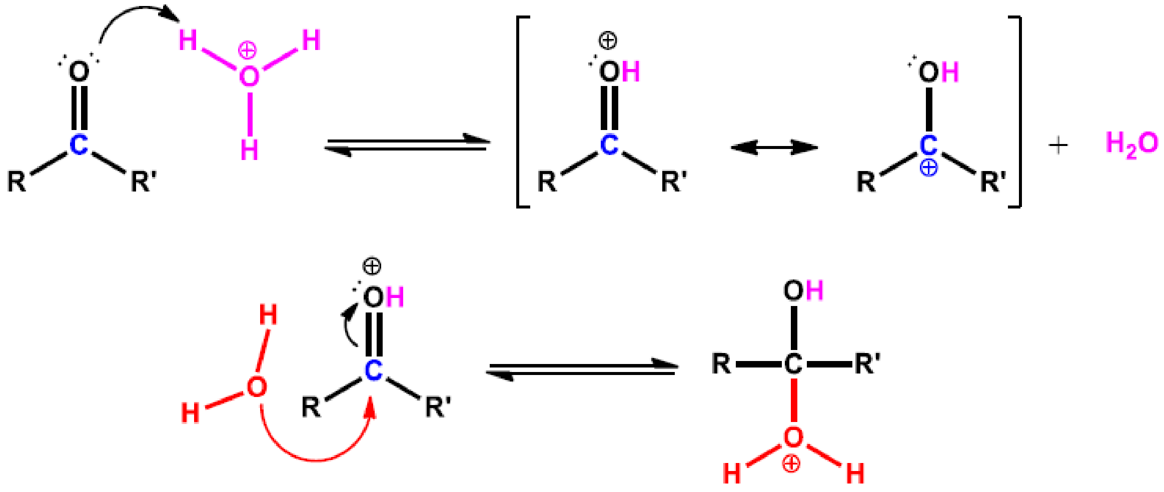
Formation of Hydrates

Hydration of aldehydes and ketones is a reversible reaction that consists in adding a water molecule to the carbonyl group, which gives germinal diols.



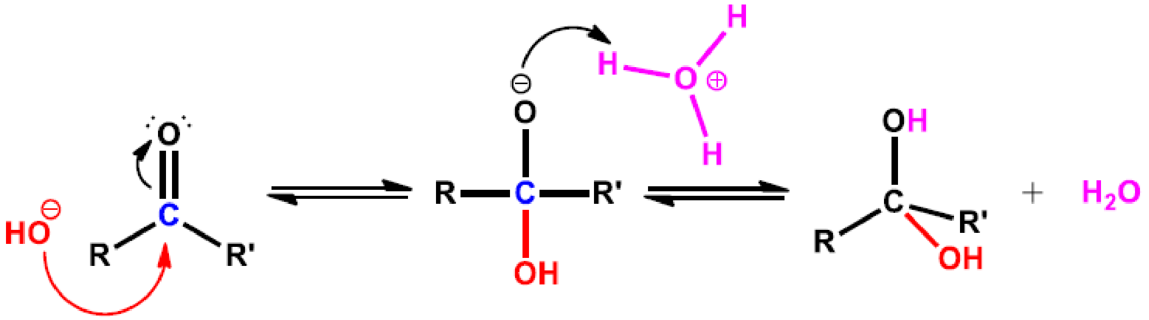
Because water is a weak nucleophile, this reaction must be catalyzed with an acid or base catalyst, and it proceeds in two reversible steps.

Under the acidic aqueous condition, the oxygen atom of carbonyl gets protonated resulting in an activated carbonyl carbon. At this point, a water molecule can easily add to the carbonyl carbon resulting in an ionic tetrahedral intermediate.



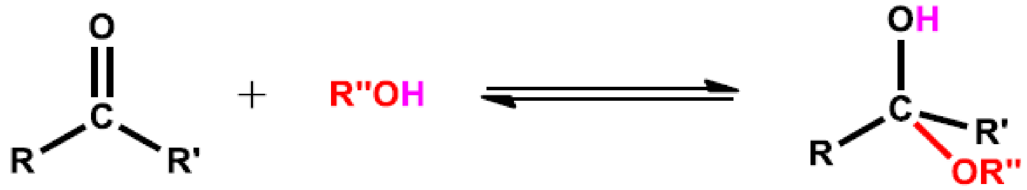
In the next step, a nearby basic species such as water, would abstract a hydrogen proton from the protonated hydroxy group and leads to the formation of a germinal diol.

Base-catalyzed hydration proceeds in a different way. Initially, the strong nucleophile HO^- adds to the carbonyl carbon resulting in a tetrahedral anionic intermediate, which then gets protonated to give the corresponding germinal diol.



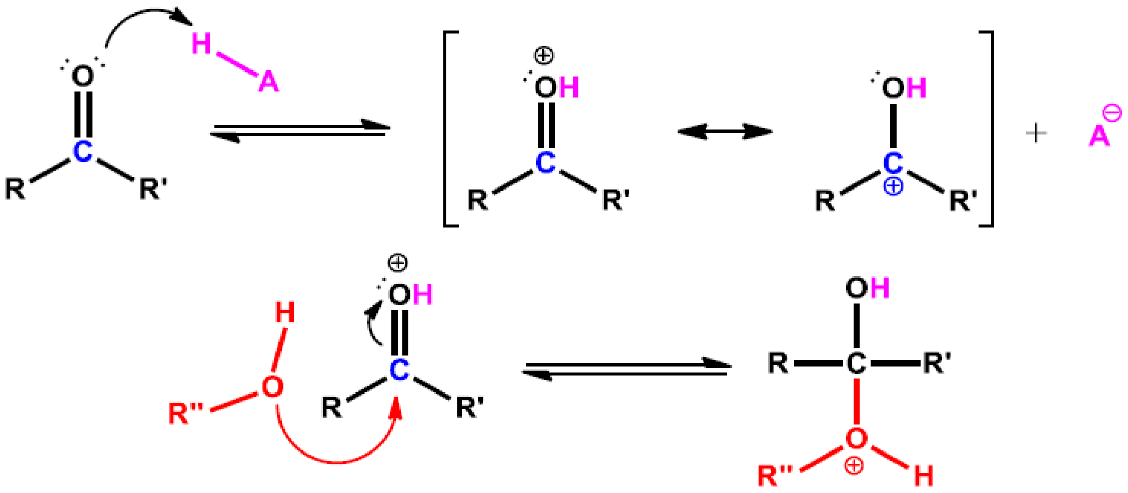
Formation of Hemiacetals, Hemiketals, Acetals, and Ketals

Formation of hemiacetals and hemiketals occurs when one equivalent of an aldehyde or ketone reacts with one equivalent of alcohol. Since the nucleophile involved is not sufficiently strong to attack the carbonyl carbon, these reactions are carried out under acidic or basic conditions. However, acid-catalyzed reactions tend to be more efficient and faster.

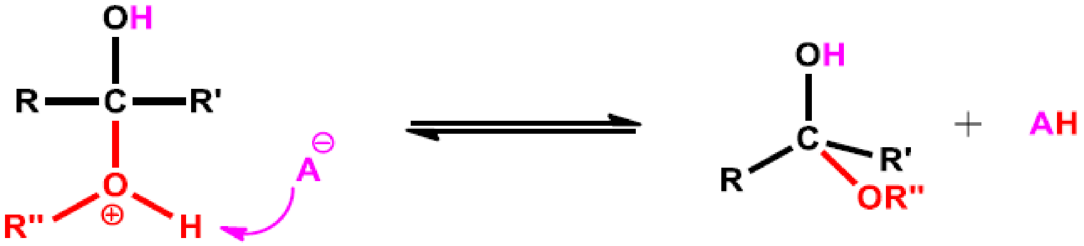


R' = H: aldehyde, hemiacetal
R' = Alkyl or aryl: Ketone, hemiketal

Initially, the oxygen atom of the carbonyl abstracts a hydrogen proton from the acid catalyst resulting in an activated carbonyl carbon. Later, a nucleophilic attack would take place. At this point, the alcohol would add to the carbonyl carbon forming, this way, an ionic tetrahedral intermediate.

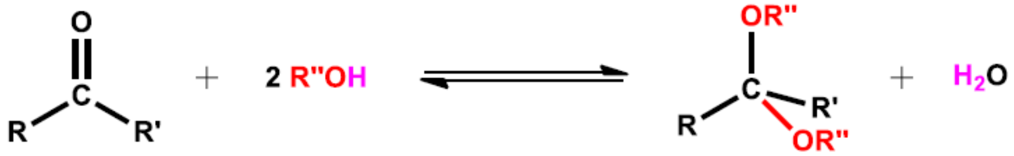


Finally, the conjugate base of the acid catalyst would deprotonate the ionic tetrahedral intermediate, which leads to the final product, hemiacetal for aldehyde, or hemiketal for ketone.

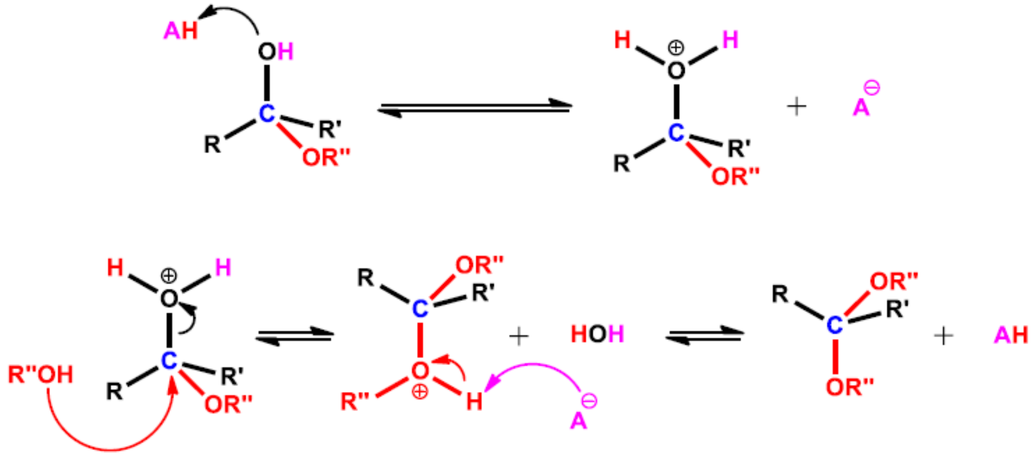


Furthermore, it is essential to know that all these reactions are reversible. Nevertheless, for aldehydes, the equilibrium tends to shift towards the hemiacetal. On the other hand, because hemiketals are more reactive than ketones, the equilibrium tends to shift towards ketones instead of hemiketals.

If one equivalent of an aldehyde or ketone reacts with two equivalents of alcohol, the reaction does not stop and the hemiacetal or hemiketal undergoes a nucleophilic substitution in which hydroxy groups get displaced by an alkoxy group. In this case, aldehydes would produce acetals while ketones would give ketals.



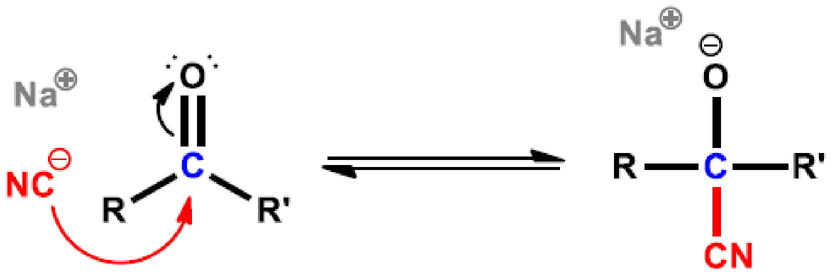
R' = H: aldehyde, acetal
R' = Alkyl or aryl: Ketone, ketal



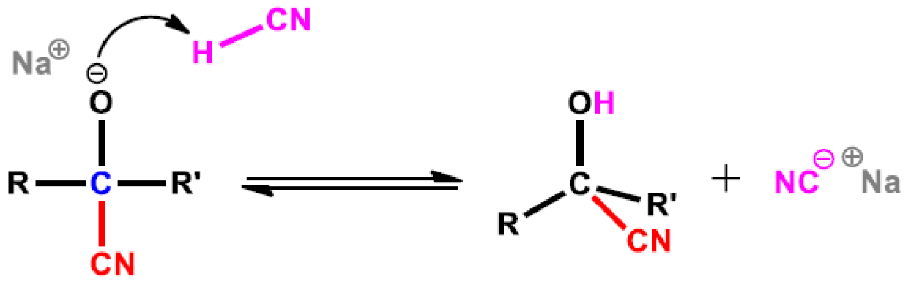
Formation of Cyanohydrins

Cyanohydrin synthesis is accomplished by treating an aldehyde or ketone with cyano ions in a buffered solution. This reaction proceeds via nucleophilic addition in two reversible steps and follows the first-order kinetics.

The first step of cyanohydrin formation is characterized by the nucleophilic addition of the cyano ion to the carbonyl carbon atom. In this case, cyano ions are sufficiently nucleophilic to attack the partially positive carbonyl carbon atom resulting in an ionic tetrahedral intermediate.

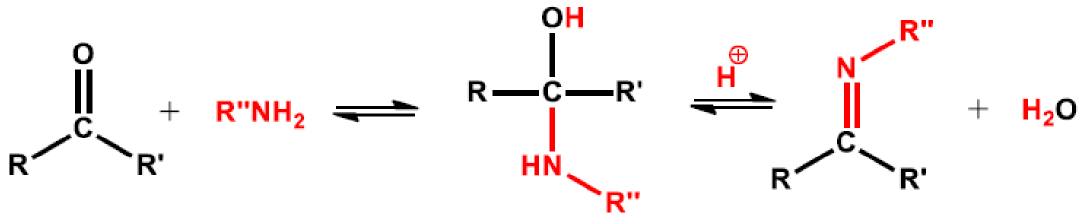


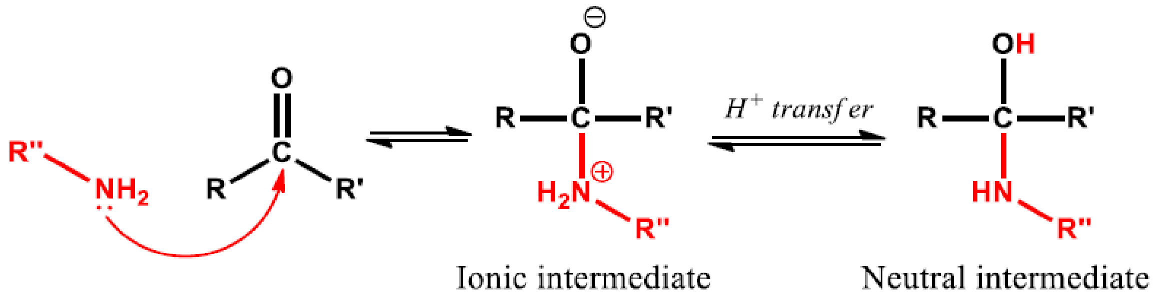
The second step consists in protonating the alkoxy group, which leads to the formation of the corresponding cyanohydrin.



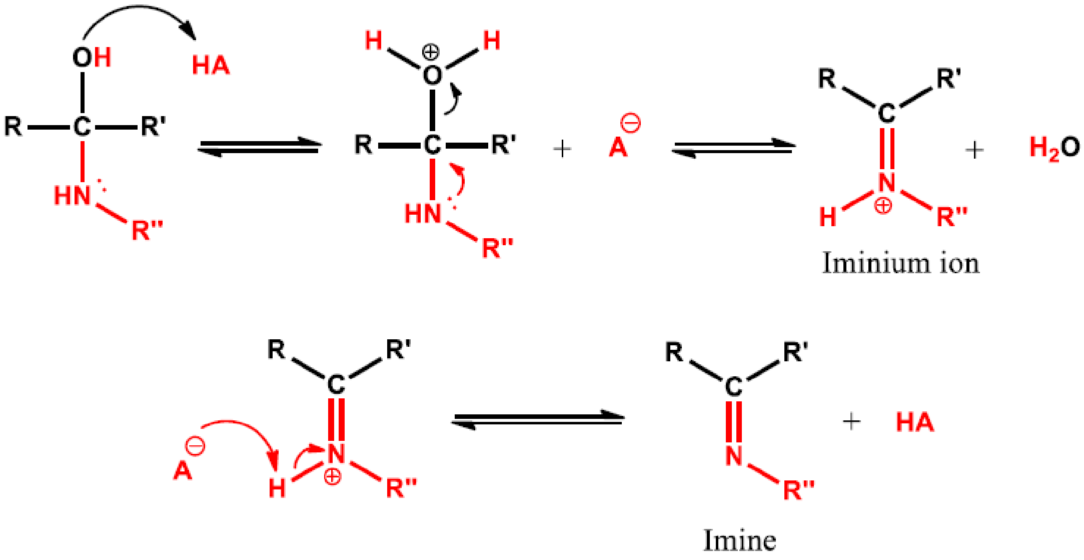
Formation of Imines and Enamines

Aldehydes and ketones react with primary amines to produce imines. This reaction proceeds in two reversible steps; initially, and often without a catalyst, the primary amine attacks the carbonyl carbon resulting in an ionic tetrahedral intermediate, which eventually transforms into a neutral one after a hydrogen transfer.

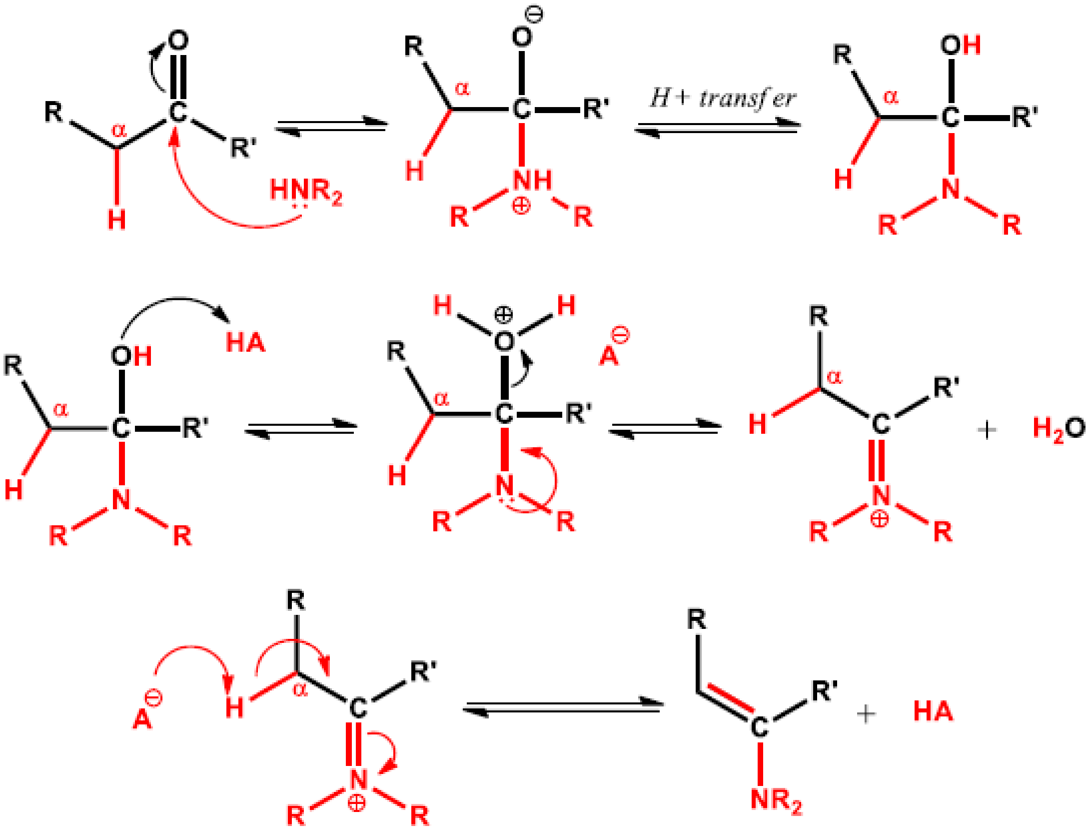




The next step consists in dehydrating the neutral intermediate under acidic conditions leading to the final product “imine”.



When secondary amines react with aldehydes or ketones, the reaction proceeds in a similar way. However, since the iminium ion has no available hydrogen atom attached to the nitrogen, which is supposed to be abstracted in the second step, the reaction proceeds in a different way. In this case, if there is an available hydrogen on the α carbon atom, it can be removed leading to the formation of an enamine.



Enamine

Electrophilic Addition Reactions

Electrophilic addition reactions are the most characteristic reaction of alkenes and alkynes. These reactions involve electrophiles and pass through the formation of ionic intermediates. Moreover, electrophilic addition reactions are so important in organic chemistry synthesis since they interconvert alkenes and alkynes into other important functional groups.

General mechanisms

Depending upon the type of electrophile used, electrophilic reactions differ from one another. However, they all proceed in two steps and pass through the formation of an ionic intermediate. The first step is a slow process in which the electrophile adds to a sp2 or sp carbon atom resulting in an ionic intermediate.

The next step is a fast process where a nucleophilic species adds to the neighboring sp2 or sp carbon atom.

Regeochemistry and Stereochemistry

Electrophilic addition reactions have different properties regarding regiochemistry and stereochemistry. In general, reactions that involve asymmetrical reagents are regioselective that follow Markovnikov's rule.

Markovnikov's rule

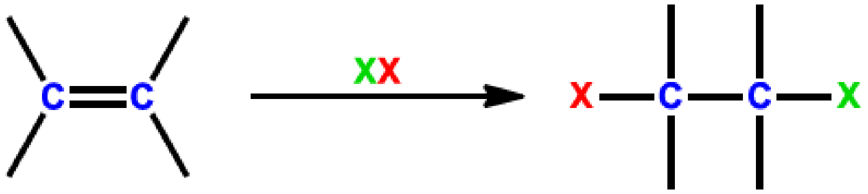
Markovnikov's rule is used to study the regiochemistry of electrophilic reactions. It helps in predicting which adduct would prevail over the others. According to Markovnikov's rule, electrophiles preferentially add to the most hydrogenated carbon atom to produce the most stable ionic intermediate and product.

Di-halogenation Reaction

Di-halogenation is an electrophilic addition reaction where two identical halogens XX add to a substrate across multiple bonds. This reaction can occur in both alkenes and alkynes.

Alkenes

Alkenes react with di-halogens to produce vicinal alkyl halides. In this case, the π bond breaks and each sp2 carbon atom binds to a halogen atom.

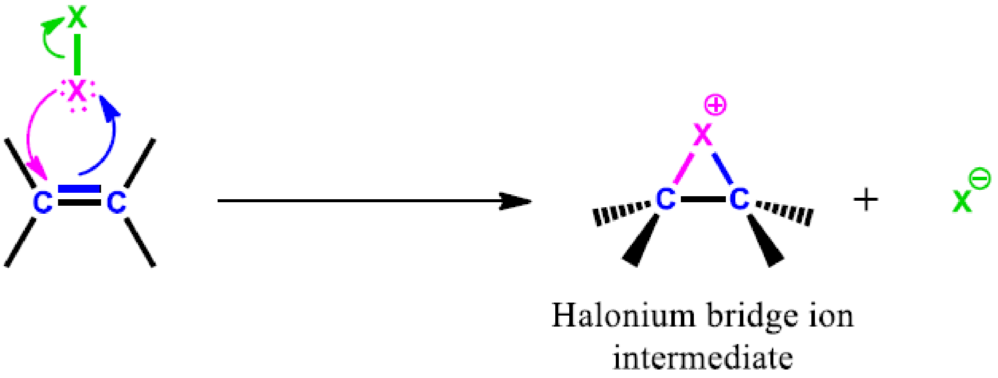


Mechanism

The addition of identical halogens to alkenes proceeds in two steps and involves an ionic intermediate.

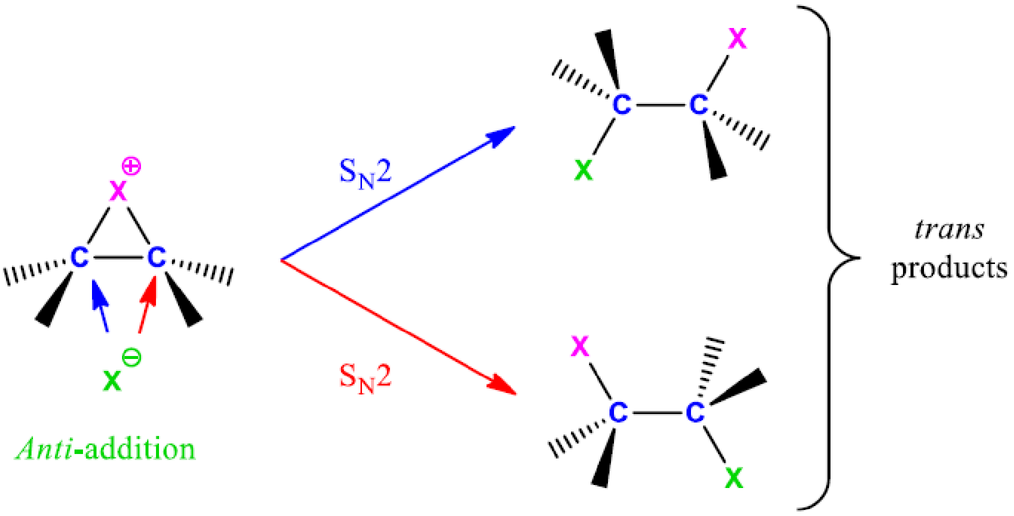
Step one

Initially, the electrophilic halogen adds to the π bond resulting in a cyclic ionic intermediate known as a halonium bridge ion and a halide ion.



Step two

In the next step, the nucleophilic halide ion would attack one of the carbon atoms of the cyclic intermediate, which leads to opening the cycle and forming vicinal alkyl halide. This step is analogous to the S_N2 reaction, and the nucleophilic attack can only occur via *anti*-addition.



Regiochemistry and Stereochemistry

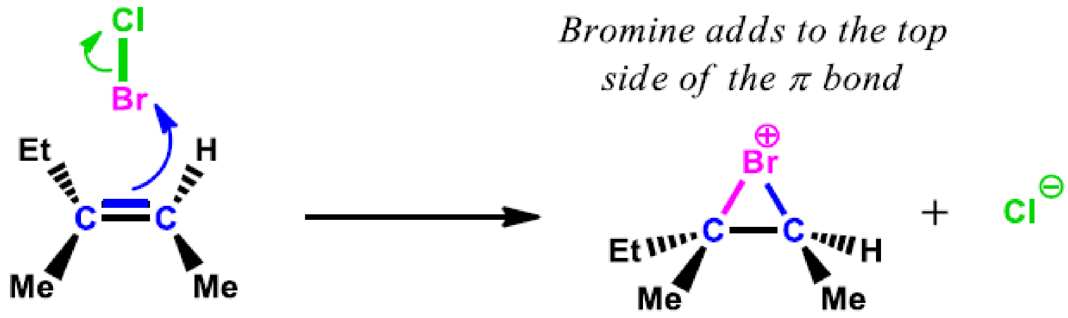
Halogenation reaction is a **regioselective reaction** that does respect Markovnikov's rule where the major product is the one obtained when the least electronegative halogen "electrophile" adds to the most hydrogenated carbon atom. On the other hand, the most electronegative halogen adds to the least hydrogenated carbon atom. Furthermore, halogenation of alkenes is a **regiospecific reaction** that proceeds exclusively via *anti*-addition.

Example

Bromochlorination of (*E*)-3-methylpent-2-ene will give a saturated hydrocarbon with bromine and chlorine attached to vicinal carbon atoms.

Step one

Since chlorine has a higher electronegativity than bromine, it would withdraw the bonding electrons toward its nucleus resulting in a partial positive charge on the bromine. As a result, bromine will act as an electrophile and add to the π bond to form a bromonium ion bridge.

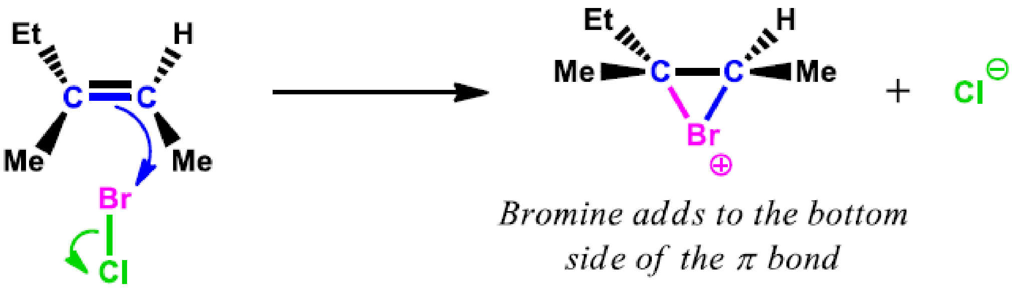


Bromine adds to the top side of the π bond

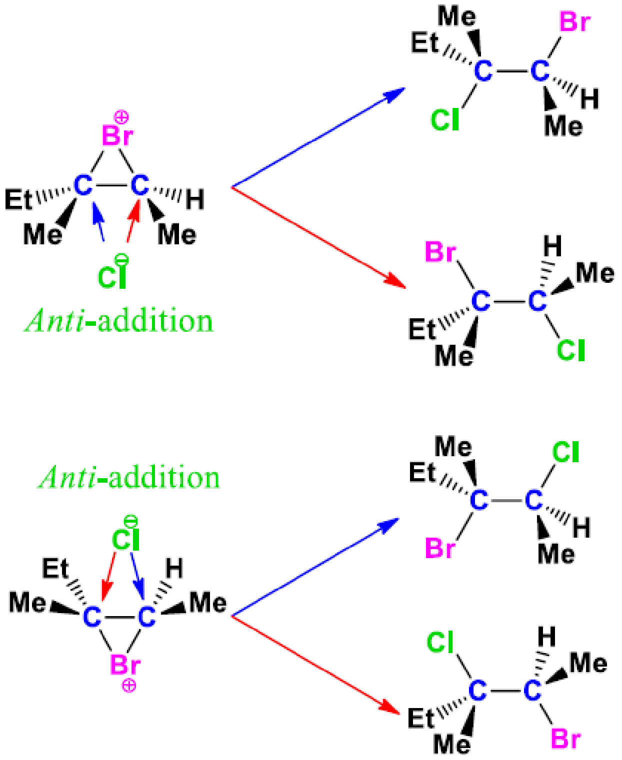
(*E*)-3-methylpent-2-ene

Step two

(*E*)-3-methylpent-2-ene



In the next step, the chloride ion would preferentially attack the most substituted carbon atoms attached to the bromonium ion via *anti*-addition.



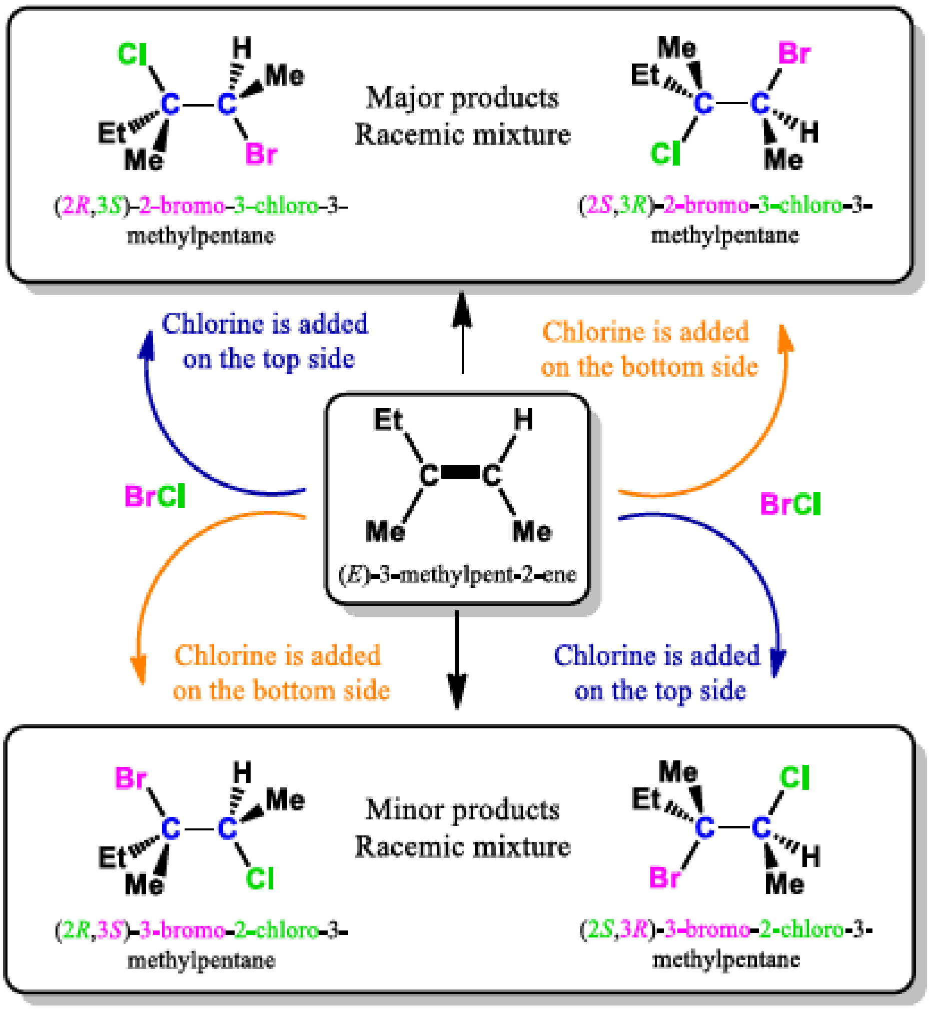
(2*S*,3*R*)-2-bromo-3-chloro-3-methylpentane
Major product

(2*R*,3*S*)-3-bromo-2-chloro-3-methylpentane
Minor product

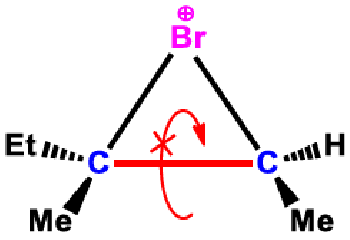
(2*S*,3*R*)-3-bromo-2-chloro-3-methylpentane
Minor product

(2*R*,3*S*)-2-bromo-3-chloro-3-methylpentane
Major product

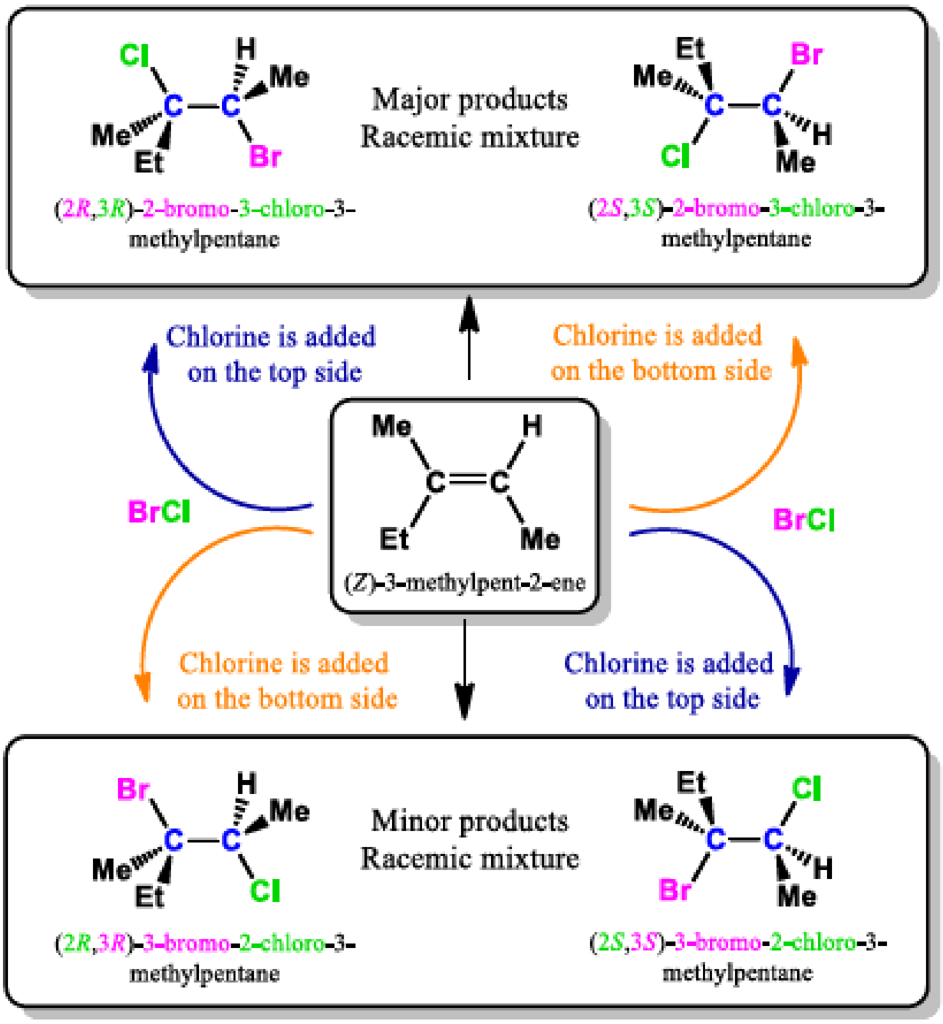
The overall reaction would then give two racemic mixtures with one more predominant. As a result, halogenation of asymmetrical alkenes is a **non-stereoselective** reaction.



Because the intermediate involved is cyclic, free rotation around the σ bond connecting the two carbon atoms attached to the bromonium ion is not possible. Consequently, (*Z*)-3-methylpent-2-ene reacts with bromine chloride to yield the same products obtained when using (*E*)-3-methylpent-2-ene. Nevertheless, these compounds would have different stereochemistry, which makes this reaction **stereospecific**.

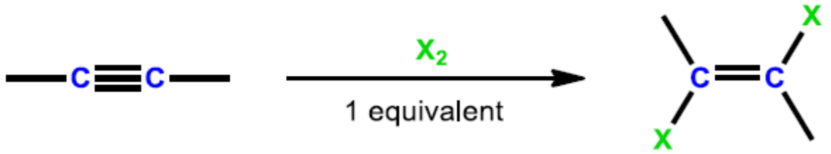


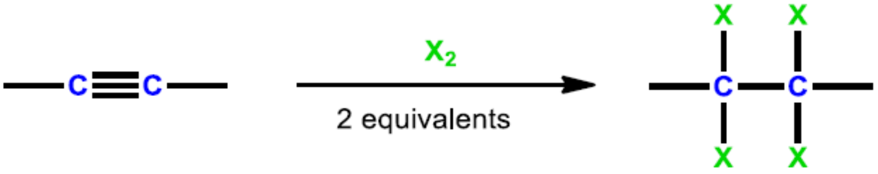
Rotation around σ bond is not allowed.



Alkynes

Unlike alkenes, alkynes have two π bonds, which makes them susceptible to further electrophilic addition. As a result, dihalogenation of alkynes can yield either a dihalogenated alkene or an alkyl tetrahalide depending upon the reaction condition. Alkynes react with one equivalent of a dihalogen to give trans-dihalogenated alkenes. However, when two equivalents of dihalogen react with one equivalent of alkynes, alkyl tetrahalide is obtained.



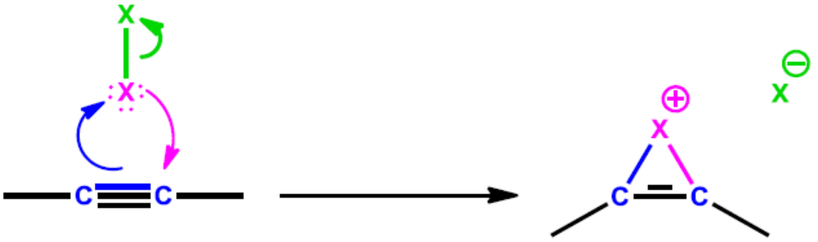


Mechanism

The mechanism of alkynes halogenation is like that of alkenes. It proceeds in two steps and involves a halonium bridge ion intermediate.

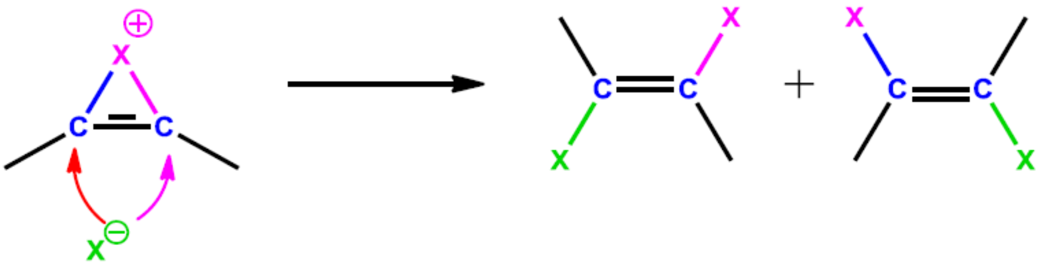
Step one

Addition of the electrophile and formation of cyclic ionic intermediate.

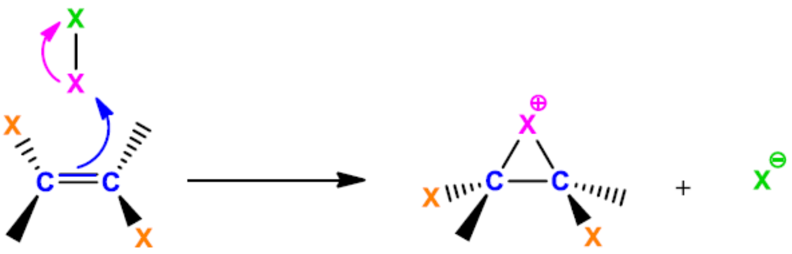


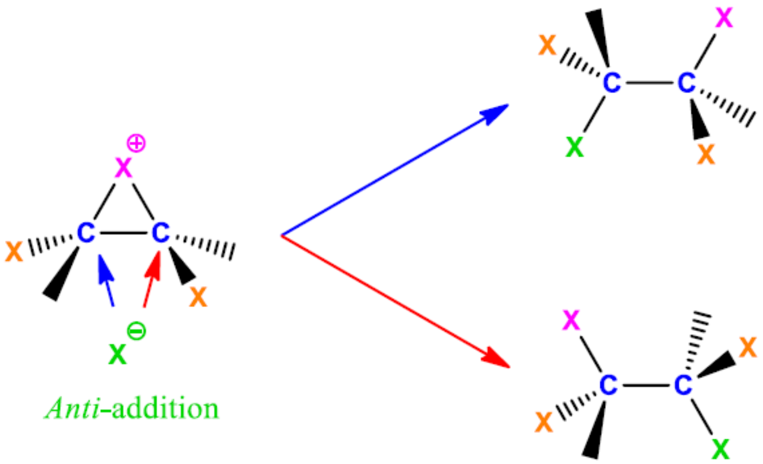
Step two

The next step is characterized by the *anti*-addition of the nucleophilic halide, which leads to *trans*-dihalide alkene.



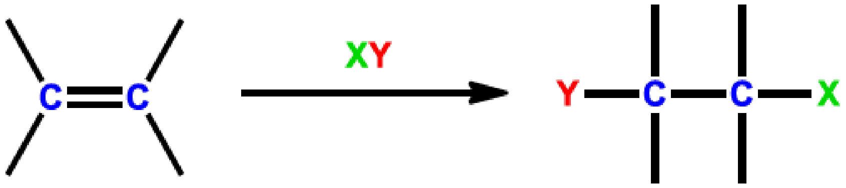
If the reaction is performed with two molecular equivalents of the dihalide, further dihalogenation would take place resulting in an alkyl tetrahalide is formed.





Halogenation Reaction

Halogenation of alkenes is an electrophilic addition where two different halogens XY add to a substrate across the multiple bonds.

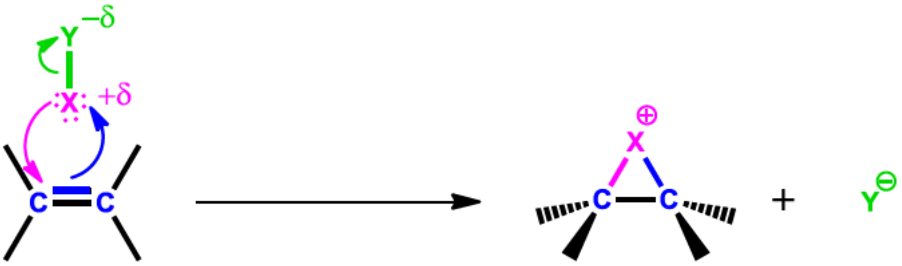


Mechanism

Halogenation of alkenes follows the same mechanism of dihalogenation. It proceeds in two separated steps and involves a halonium ion intermediate to produce a vicinal dihalide alkanes.

Step one

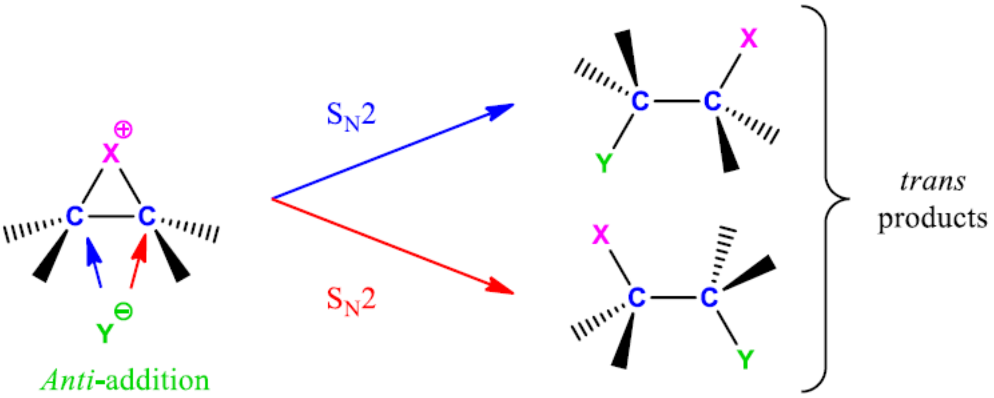
Since the dihalogen molecule is asymmetrical, the more electronegative atom would pull the bonding elections towards its nucleus, which create a dipole-dipole moment with an electron deficient side. In this case, the least electronegative halogen will act as an electrophile.



Halonium bridge ion intermediate

Second step

The second step involves the *anti*-addition of the nucleophilic halide to either carbon atoms attached to the halonium ion.



Regiochemistry and Stereochemistry

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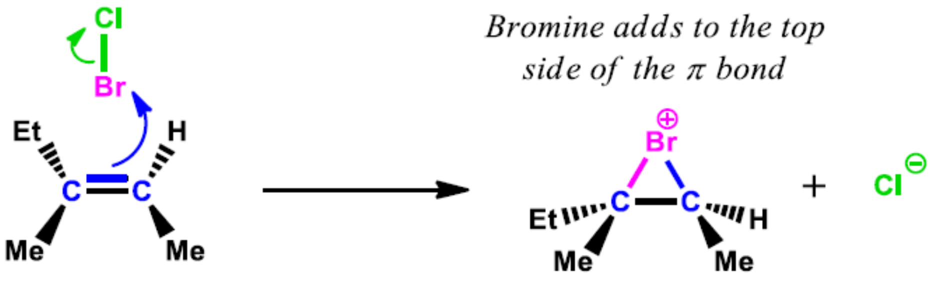
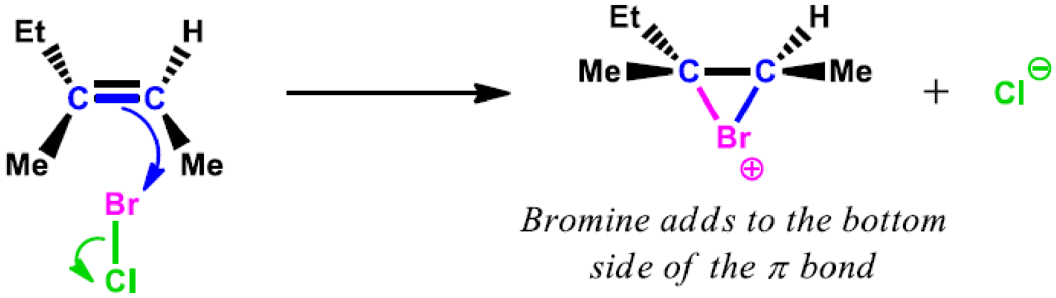


Bromine adds to the top side of the π bond

(*E*)-3-methylpent-2-ene

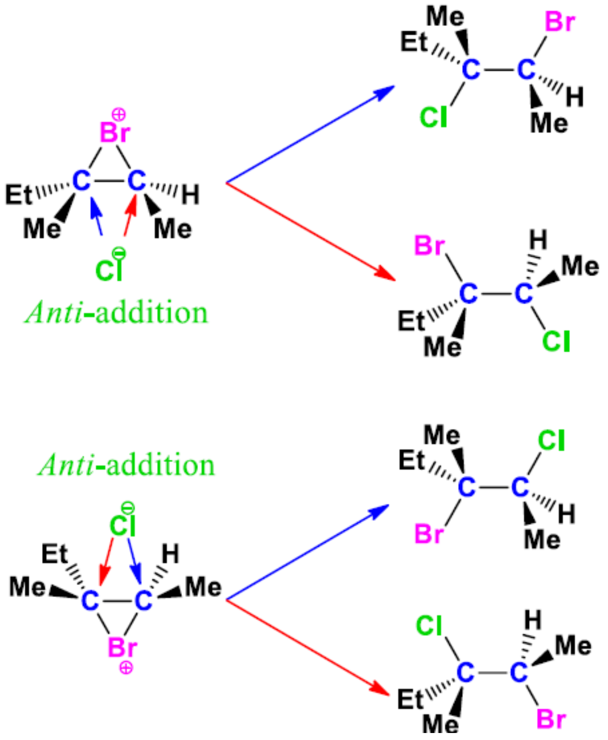
(*E*)-3-methylpent-2-ene



Bromine adds to the bottom side of the π bond

Step two

In the next step, the chloride ion would preferentially attack the most substituted carbon atoms attached to the bromonium ion via *anti*-addition.



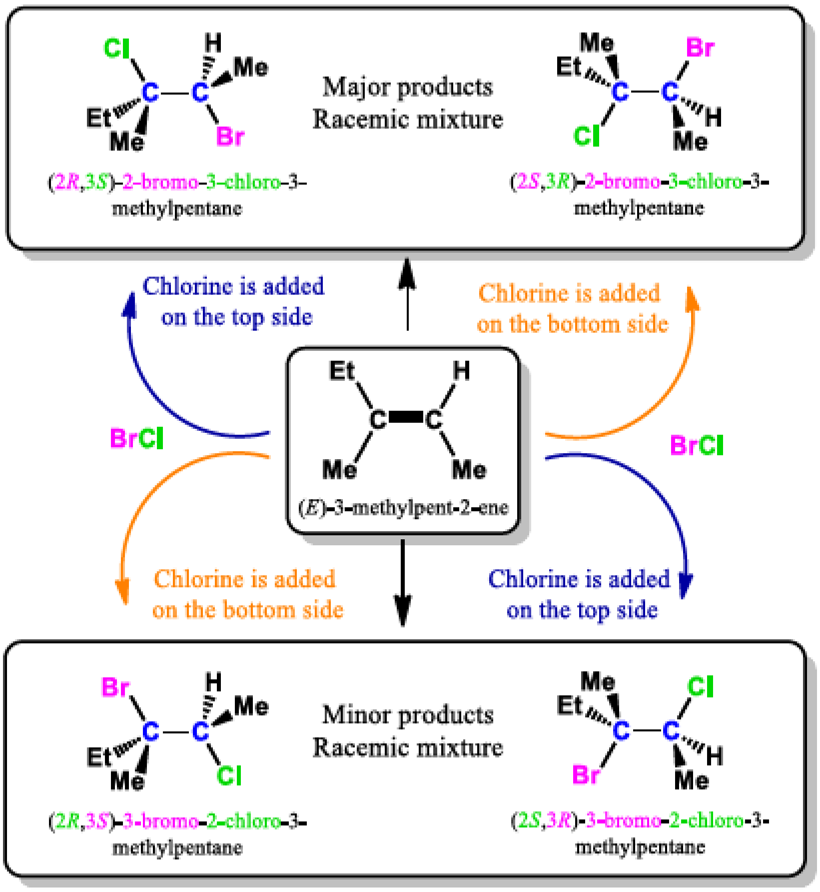
(2*S*,3*R*)-2-bromo-3-chloro-3-methylpentane
Major product

(2*R*,3*S*)-3-bromo-2-chloro-3-methylpentane
Minor product

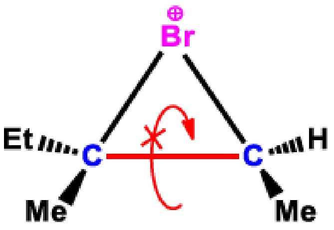
(2*S*,3*R*)-3-bromo-2-chloro-3-methylpentane
Minor product

(2*R*,3*S*)-2-bromo-3-chloro-3-methylpentane
Major product

The overall reaction would then give two racemic mixtures with one more predominant. As a result, halogenation of asymmetrical alkenes is a **non-stereoselective** reaction.



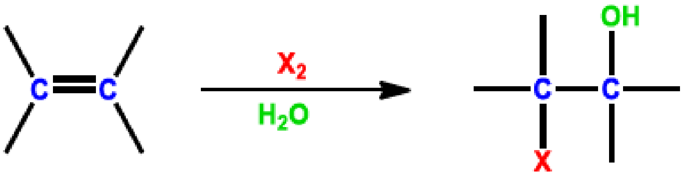
Because the intermediate involved is cyclic, free rotation around σ bond connecting the two carbon atoms attached to bromonium ion is not possible. Consequently, (*Z*)-3-methylpent-2-ene reacts with bromine chloride to yield the same products obtained when using (*E*)-3-methylpent-2-ene. Nevertheless, these compounds would have different stereochemistry, which makes this reaction **stereospecific**.



Rotation around σ bond is not allowed.

Hypohalogenation Reaction

Hypohalogenation is an electrophilic reaction that consists in converting alkenes into halohydrins. This reaction take place when using halogens such as Br_2 or Cl_2 more than water.

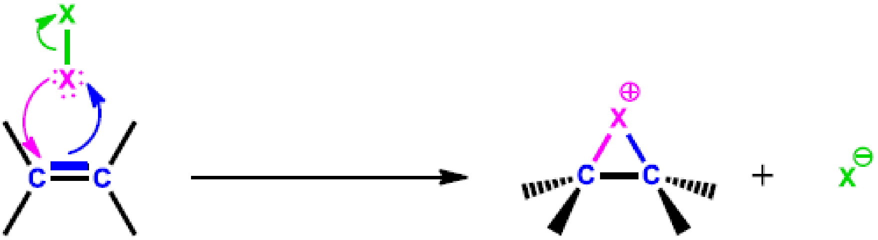


Mechanism

Just like alkenes halogenation, hypohalogenation proceeds in two steps and involves a halonium ion bridge.

First step

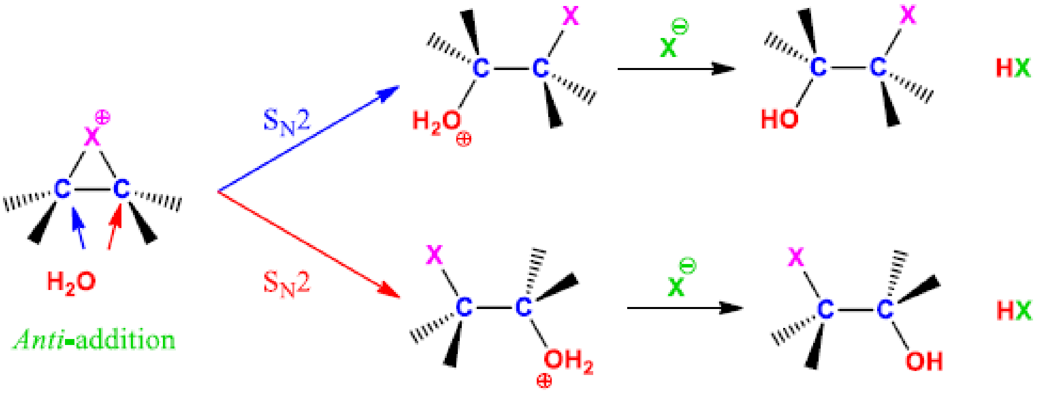
The first step consists in forming a halonium ion bridge intermediate.



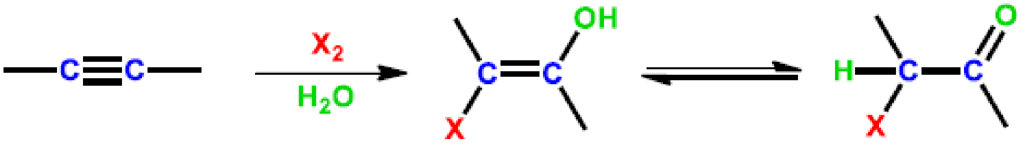
Halonium bridge ion intermediate

Second step

In the next step, a water molecule will preferentially attack the most substituted carbon atom, which leads to an oxonium intermediate. This nucleophilic attack proceeds exclusively via *anti*-addition.



In the case of alkynes, the reaction initially produces a *trans*-halogenated enol, which then tautomerizes to give α-halo carbonyl compounds.

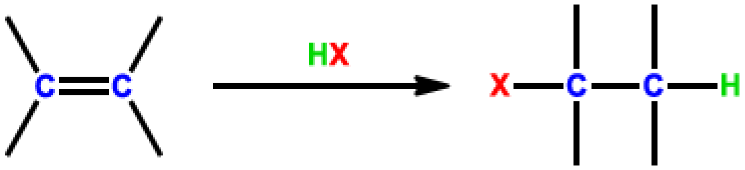


Hydrohalogenation Reaction

Hydrohalogenation is an electrophilic addition that consists in adding a hydrogen atom and a halogen to two carbon atoms of a substrate that relate to a multiple bond. These carbon atoms may or may not be vicinal depending upon the structure of the substrate and the possibility of carbocation rearrangement s. Hydrohalogenation reaction involves hydrogen halide acids such as HI, HBr, and HCl where hydrogen acts as an electrophile while halogens act as nucleophiles.

Alkenes

In the case of alkenes, the hydrogen atom and halide are generally added to the vicinal sp2 carbon atoms. However, sometimes the addition occurs on non-vicinal carbon atoms due to carbocation rearrangement.

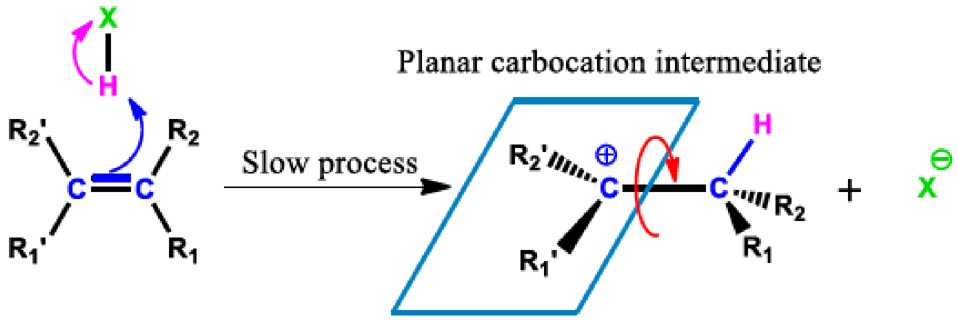


Mechanism

Hydrohalogenation reaction proceeds in two steps and involves a carbocation intermediate.

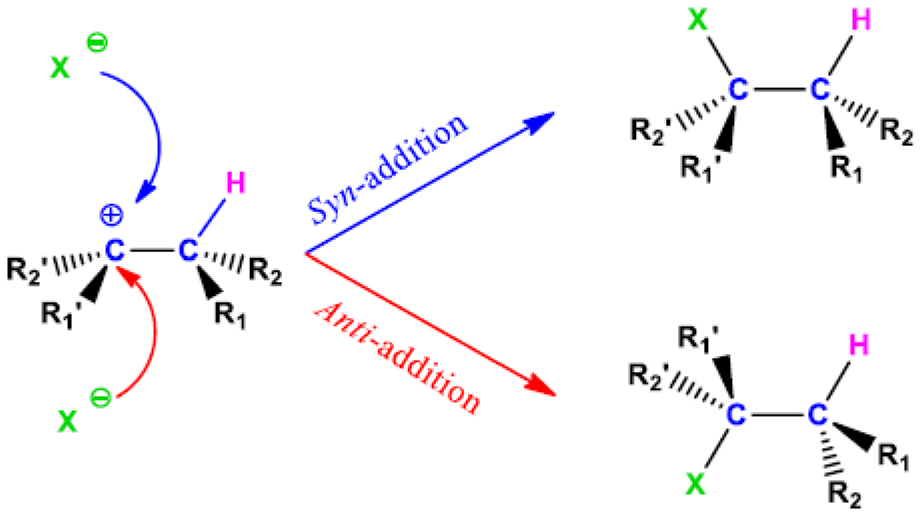
Step one

The first step is a slow process in which the π bond breaks and abstracts a hydrogen proton from the hydrogen halide resulting in a carbocation intermediate and a halide ion.



Step two

The second step is a fast process where the nucleophilic halide attacks the carbocation from either side. This process proceeds via *syn*-addition and *anti*-addition.



Regiochemistry and Stereochemistry

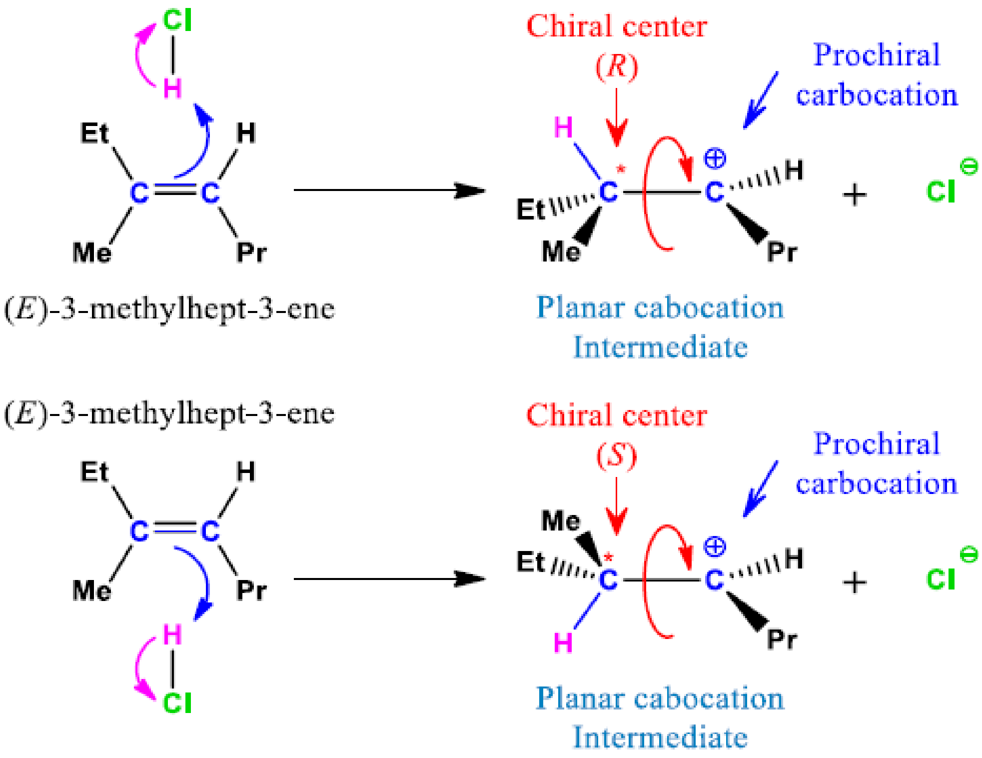
Hydrohalogenation addition is a **regioselective reaction** that follows Markovnikov's rule. In this reaction, the hydrogen atom "electrophile" preferentially adds to the least substituted carbon atom while the nucleophilic halide adds to the most substituted one. Moreover, hydrogen atoms and halide can be added to the substrate via *syn*-addition or *anti*-addition resulting in two different configurations on the corresponding stereocenter therefore hydrohalogenation is a **non-regiospecific, non-stereoselective reaction**. Moreover, since this reaction involves a carbocation intermediate where the free rotation around σ the bond is not restricted, the initial configuration of the alkene is not preserved and as a result, hydrohalogenation of asymmetrical alkenes is a **non-stereospecific reaction**.

Example

Hydrochlorination of (*E*)-3-methylhept-3-ene

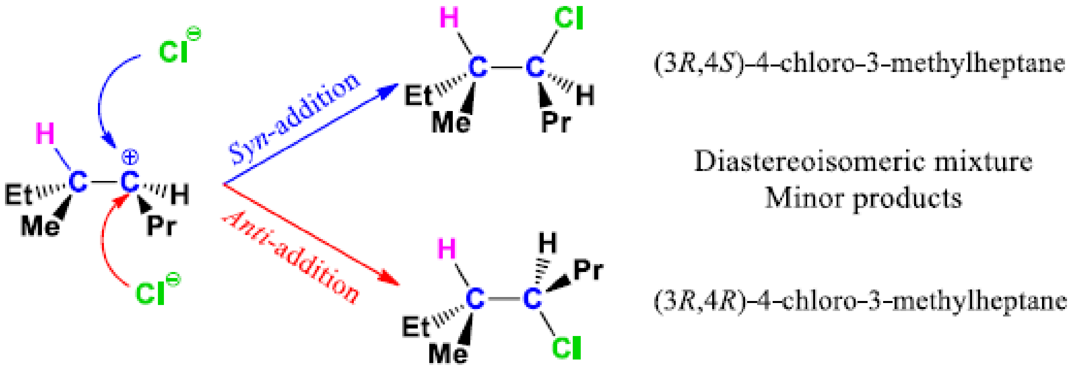
First step

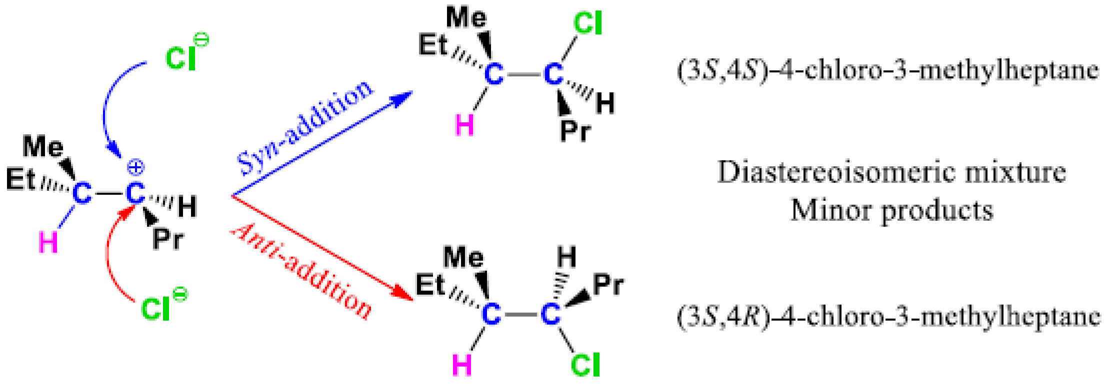
The first step consists of the protonation of one sp2 carbon atom and the formation of a carbocation intermediate and the formation of a chloride ion. In this case, the hydrogen atom was added to the most substituted carbon atom and thus, producing the least stable carbocation. Moreover, hydrogen protons can be added from either side of the π bond, which leads to the formation of two different stereocenters.



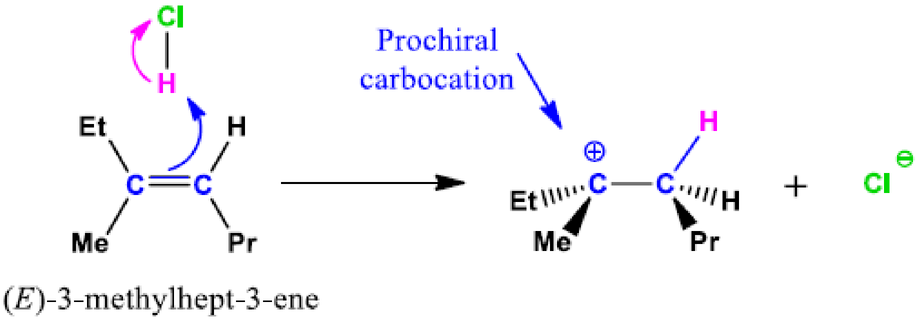
Second step

In this step, the chloride ion would attack the carbocation from either side resulting in a mixture of two diastereoisomers. In this case, the two diastereoisomers formed are the minor products since they do not obey Markovnikov’s rule.

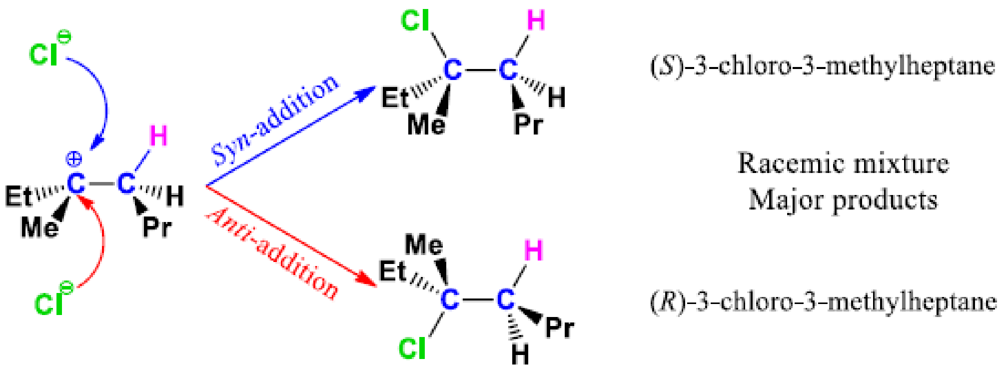




In the second case, the hydrogen atom adds s to the least substituted carbon atom, which leads to the formation of the most stable carbocation intermediate. In this case, Markovnikov's rule is respected.



Next, chloride would attack the carbocation from either side leading to a racemic mixture. In this case, Markovnikov's rule is respected and therefore, the racemate formed is the major compound.

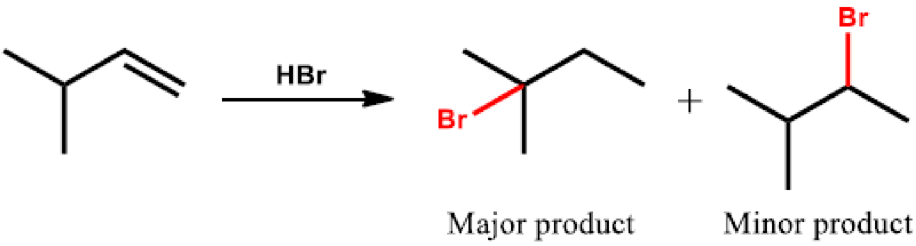


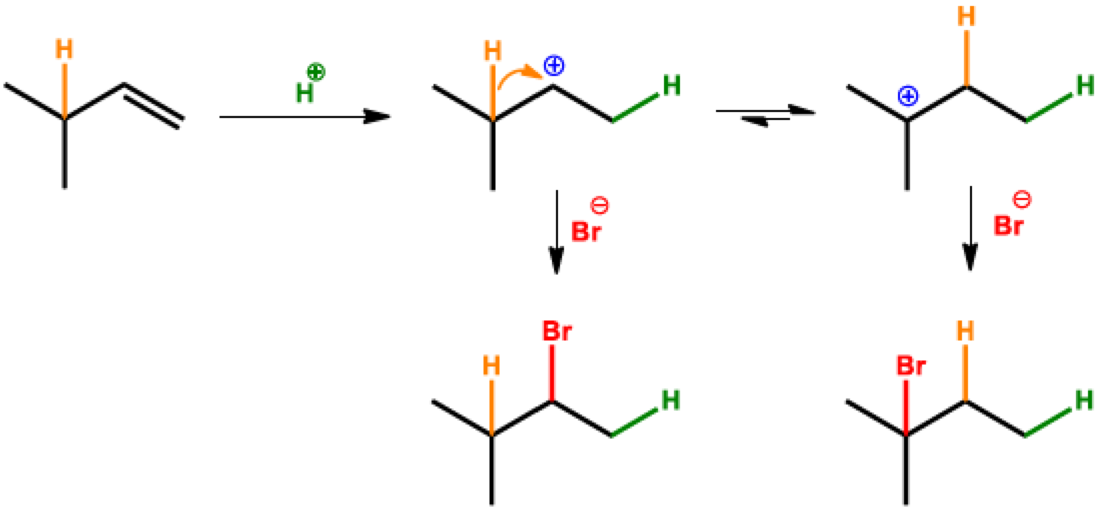
Carbocation rearrangement

Since hydrohalogenation involves a carbocation intermediate, it is important to consider the possibility of carbocation rearrangements, which affect the regiochemistry of the reaction.

Example

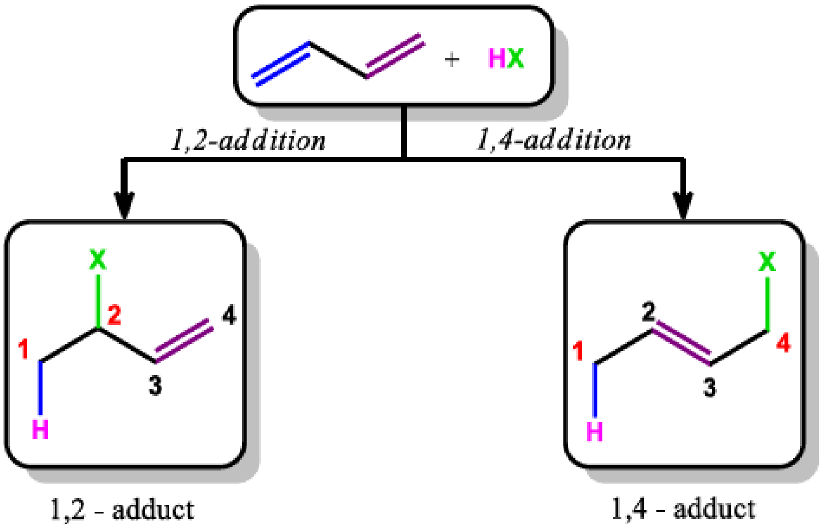
Hydrobromination of 3-methylbut-1-ene yields two constitutional isomers “regioisomers”. In this case, carbocation rearrangement.





Conjugated Dienes

Depending upon the reaction conditions, hydrohalogenation of conjugated dienes can proceed in two different manners: 1,2-addition and 1,4-addition.



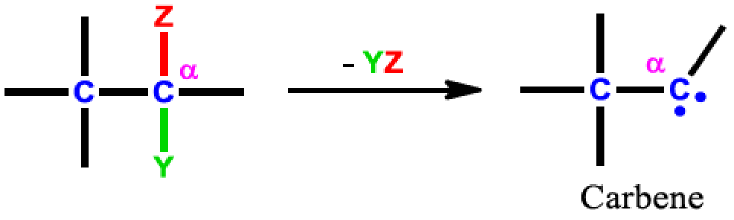
Elimination Reactions

Elimination reactions consist of removing two groups Y and Z from within a substrate. In most cases, Y is a hydrogen atom whereas Z is an electron-withdrawing group such as a halogen or hydroxy group. These two species can be attached to the same atom of the substrate or to different atoms. As a result, elimination reactions can be classified into three main categories depending on the positions of Y and Z.

- 1,1-elimination or α-elimination.
- 1,2-elimination or β-elimination.
- 1,3-elimination or γ-elimination.

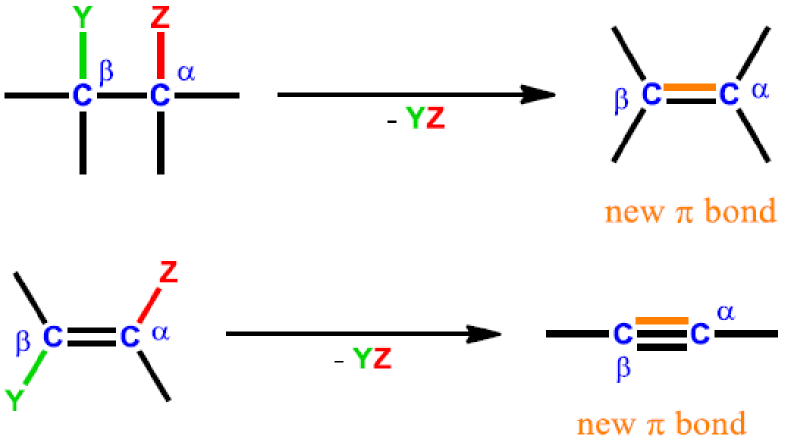
1. α - Elimination Reactions

α-elimination reaction, also known as 1, 1 – elimination, describes the reaction in which both leaving groups Y and Z are removed from the same atom. This reaction generally leads to the formation of a carbene or nitrene, which are reactive species used in further reactions.



2. β - Elimination Reactions

β-elimination reactions, also known as 1, 2 - elimination reactions, are the most common type of elimination reactions. In this case, the leaving groups Y and Z are adjacent to one another, and as they get removed from the substrate, a new π bond forms between the two carbon atoms to which Y and Z were attached resulting in the formation of an alkene or alkyne.



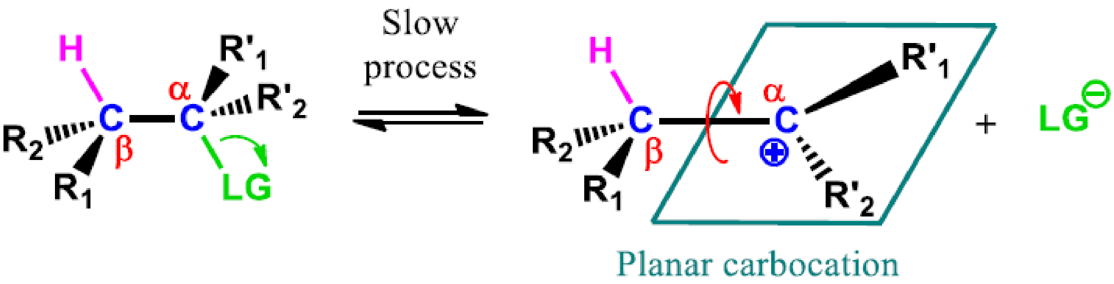
Moreover, depending upon the substrate structure and the reaction conditions. β-elimination reactions are further subdivided into three types: unimolecular elimination E1, unimolecular conjugate base elimination E1cB, and bimolecular elimination E2.

Unimolecular Elimination Reactions E1

Unimolecular elimination reaction E1 is a first-order reaction that proceeds in two steps and involves an ionic intermediate.

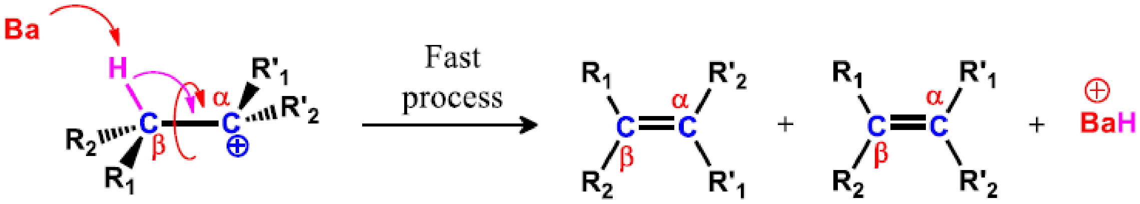
Step one

The first step is a slow reversible process whereby the bond connecting the leaving group to the substrate breaks resulting in a carbocation intermediate.



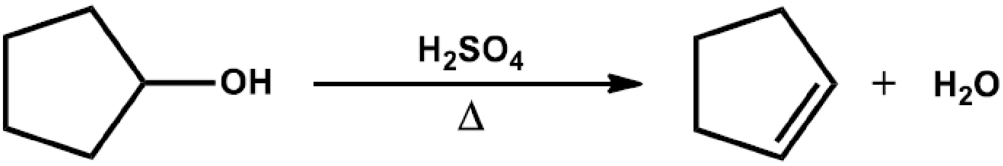
Second step

The next step is a fast process whereby a base abstract a hydrogen proton from a β-carbon atom leading to the formation of a new π bond. Since α and β carbon atoms are connected by a single bond, the free rotation around this bond is possible and therefore two diastereoisomers may form.



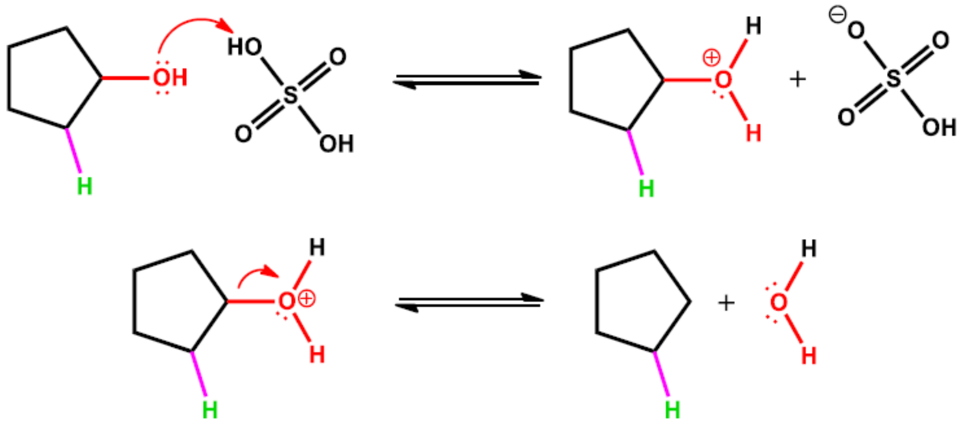
Example

When cyclopentanol is treated with a strong acid such as sulfuric acid and at high temperature, a dehydration reaction takes place via a β-elimination reaction. In this case, the reaction proceeds via the E1 mechanism due to the secondary alcohol involved.



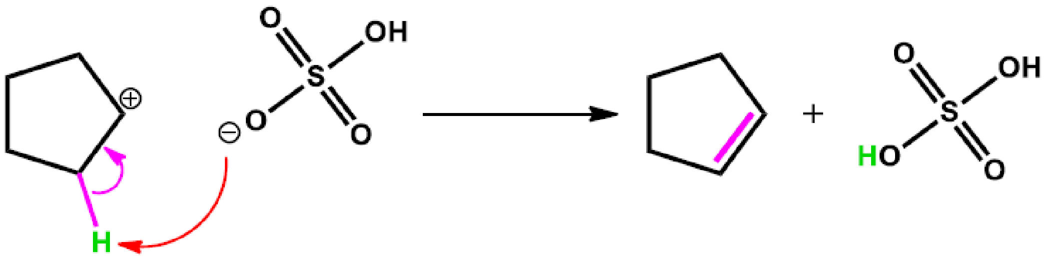
Step one

The first step consists in protonating the hydroxy group to create a better leaving group, which then gets expelled from the substrate leaving a positive charge on the carbon atom to which it was attached.



Step two

In the next step, the conjugate base of sulfuric acid would abstract a hydrogen proton from a β-carbon atom. This process will lead to the formation of a double bond between the α and β carbon atoms.



Kinetics

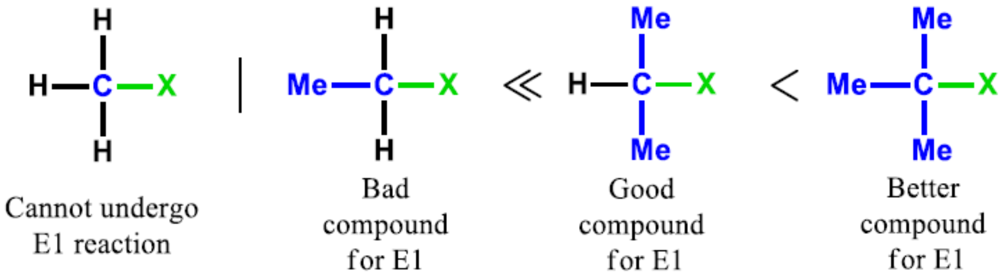
The unimolecular elimination reaction follows the first-order kinetics where the reaction rate depends solely on the substrate concentration. In this reaction, the base is not involved in the rate-determining step. As a result, increasing or decreasing the concentration of the base will not change the velocity of the reaction.

Rate = K[Substrate]

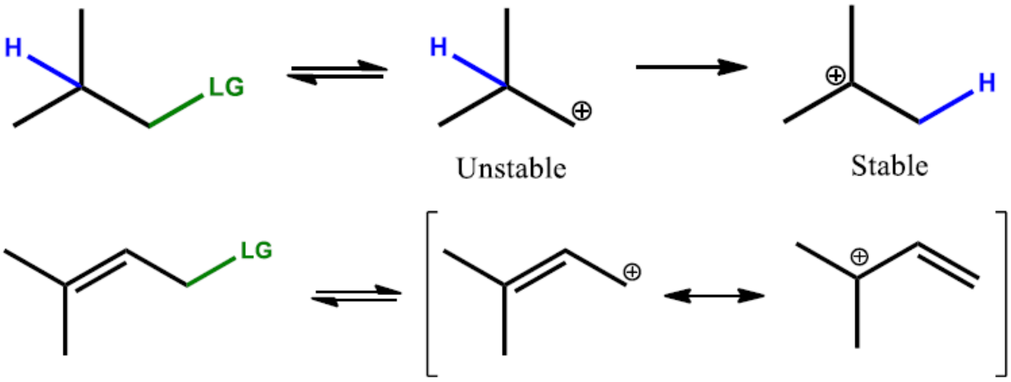
Reaction Conditions

Substrate

Since the E1 reaction involves the formation of a carbocation intermediate, tertiary substrates are more favorable for this reaction. In the case of a secondary substrate, the base must be weak to undergo an E1 reaction.



In addition, primary substrates do not undergo an E1 reaction unless the resulting carbocation can be stabilized by resonance or rearrangement.



Base

E1 reaction goes via first-order kinetics law where the rate depends only upon the concentration of the substrate. As a result, with the right substrate, an E1 reaction is possible regardless of the strength of the base. Nevertheless, it is important to note that the SN1 reaction can compete with the E1 reaction when given the right conditions. Consequently, it is better to choose a strong base but weak nucleophile, and a bulky base over a small base to avoid the SN1 path.

Solvent

The first step of the E1 path requires an ionizing agent that helps in the heterolytic cleavage of the bond connecting the leaving group to the substrate and therefore, polar protic solvents such as water, methanol, and ethanol, which can also participate as bases, do favor E1 reaction.

Leaving group

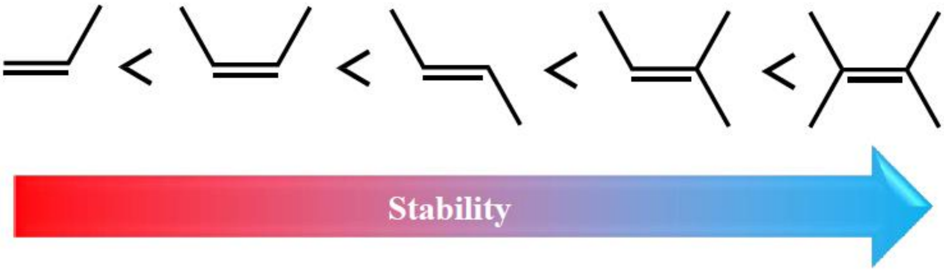
E1 reaction rate is affected by the stability of the nucleofuge. The better the leaving group, the faster the reaction. As a result, substrates that possess a good leaving group such as secondary and tertiary alkyl halides readily undergo β-elimination reaction via the E1 mechanism. On the other hand, dehydration of secondary and tertiary alcohols, which proceeds via the E1 mechanism, is catalyzed reaction where the hydroxy group is converted into a better-leaving group.

Regiochemistry and Stereochemistry

β-elimination reactions are **regioselective** reactions that favor one regio -isomer over the others. The regioselectivity of these reactions depends upon the molecular structure of the substrate, the steric hindrance of the base used, and from which β-carbon the hydrogen proton is removed. To predict which regio-isomer is more likely to form, chemists have established three main rules that focus on the regiochemistry of β-elimination re actions "Zaitsev's rule, Hoffman's rule, and Bredt's rule".

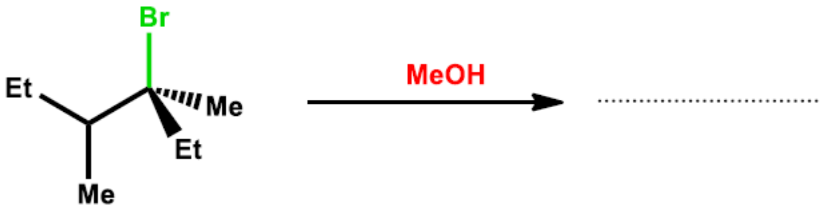
Zaitsev's Rule

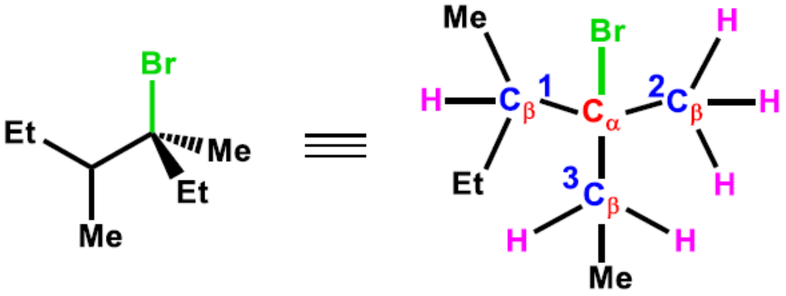
Zaitsev's rule states that in β-elimination reactions, the base preferentially abstracts a hydrogen proton from the most substituted β-carbon to give the most substituted alkene (most stable product). This rule is applied when the base involved is not sterically hindered.



Example

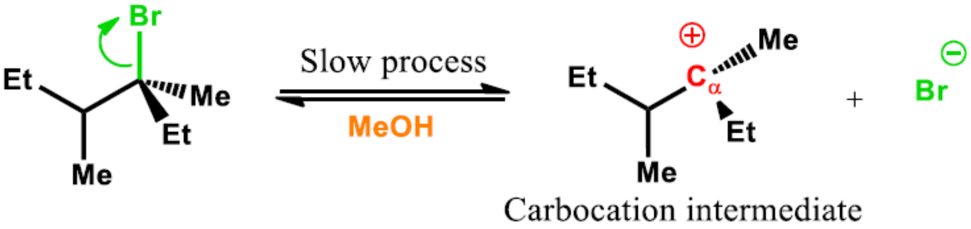
In the following example, a tertiary alkyl bromide is treated with the weak base "methanol", which also acts as a polar protic solvent. In this case, there are three available β-carbons from which a hydrogen proton can be abstracted.





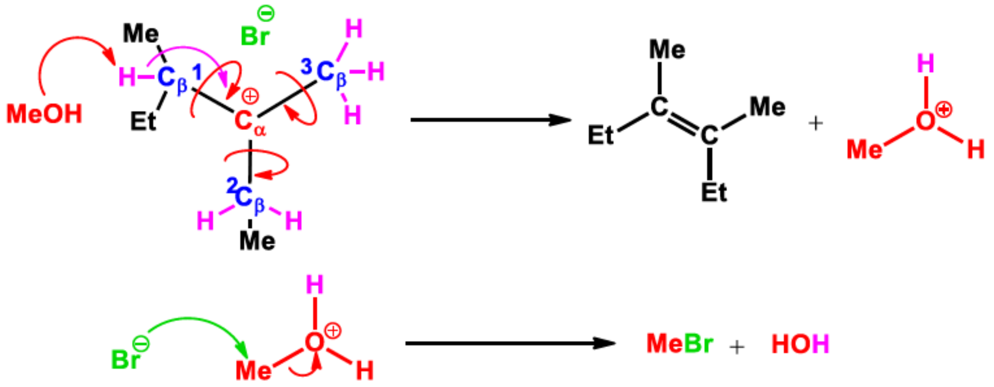
Step one

In the beginning, bromine would get expelled from the substrate with the help of the protic polar solvent “methanol” resulting in the formation of a carbocation intermediate. Since the α-carbon is tertiary, the intermediate is stabilized by the inductive donor effect of the three alkyl substituents.



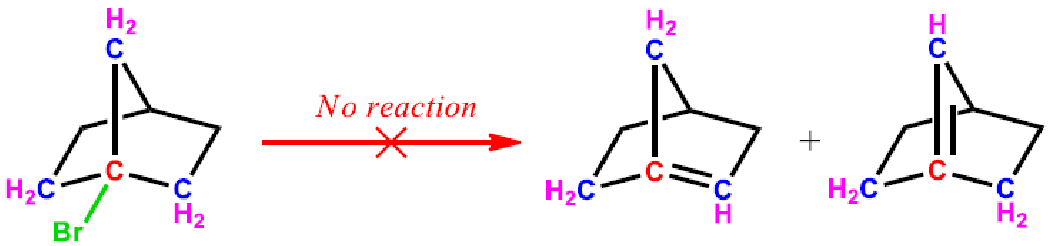
Step two

In the second step, the base “MeOH” would abstract a hydrogen proton from a β-carbon atom, which will result in the formation of an alkene. At this point, depending upon from which β-carbon the base abstracts a hydrogen proton, several products with different amounts may form. In this case, because methanol is a considerably small base, Zaitsev’s rule can be used to determine the major product(s), and a hydrogen proton is preferentially abstracted from the β-carbon 1.

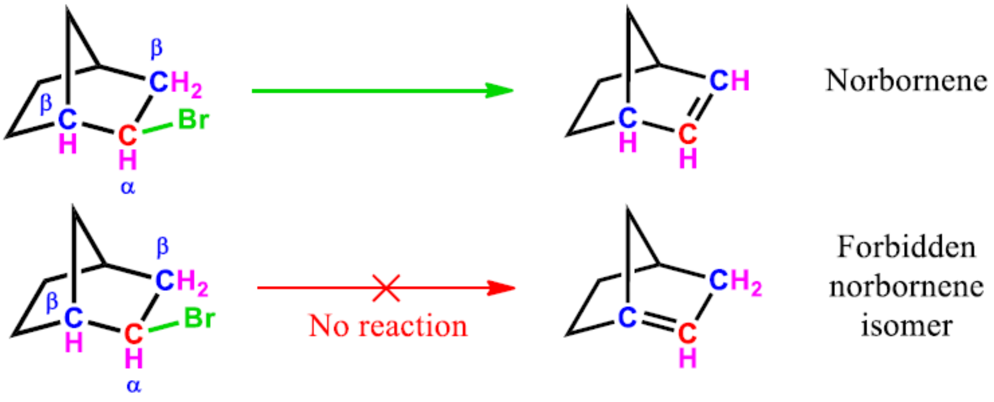


Bredt's Rule

Bredt's rule states that a double bound cannot be placed at the bridgehead carbon atom of a bridged system unless one ring is sufficiently large for the sp2 hybridized carbon atom geometry. Consequently, β-elimination reactions cannot occur when the leaving group is attached to the bridgehead atom.

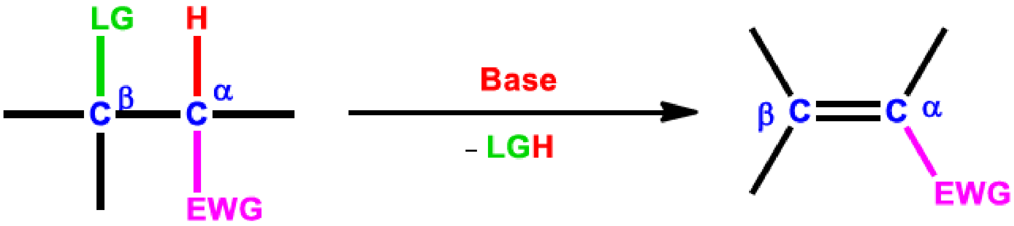


If the leaving group is attached to another carbon atom, the base would abstract exclusively the hydrogen atom attached to a peripheral β carbon atom.



Unimolecular Elimination Reaction E1cB

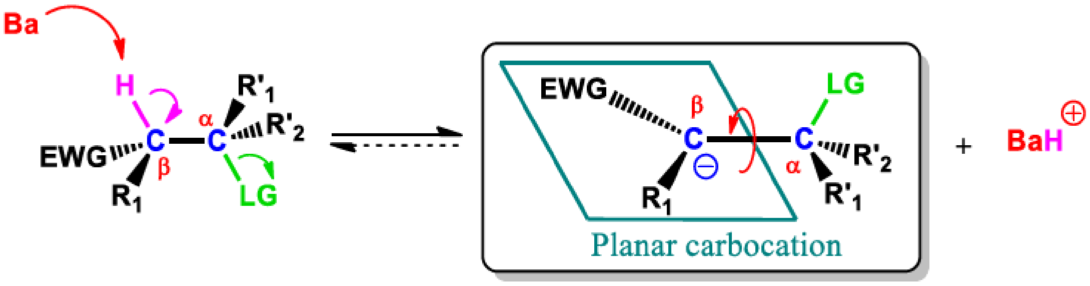
E1cB (conjugate base) reaction is a unimolecular elimination reaction that occurs under basic conditions with substrates possessing a poor leaving group such as hydroxy group -OH or alkoxy group -OR on β position, an acidic hydrogen, and an electron-withdrawing group such as carbonyl or nitro group on α position.



E1cB reaction proceeds in two steps and passes through the formation of a carbanion intermediate "conjugate base".

Step one

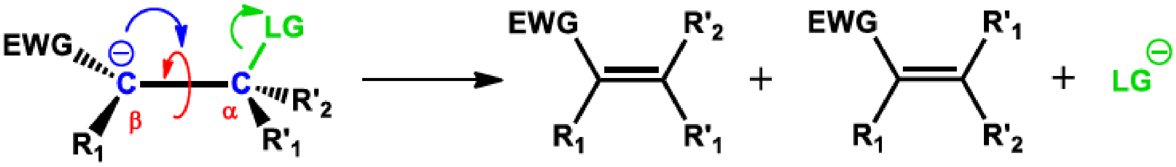
The first step is a slow process that may or may not be reversible. It is characterized by the deprotonation of the substrate with a moderate to strong base. At this point, the base would abstract the acidic hydrogen proton from the β-carbon atom resulting in a carbanion intermediate, which is also the conjugate base form of the substrate.



Conjugate base

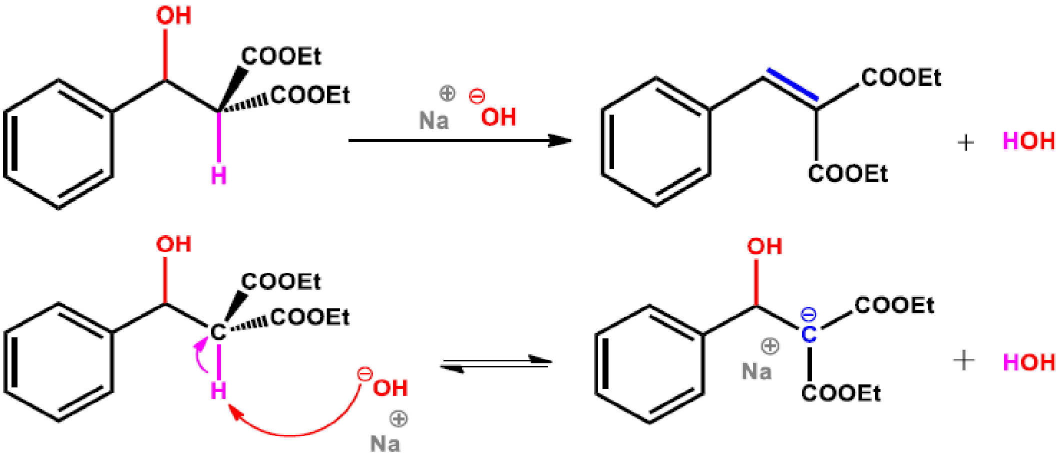
Second step

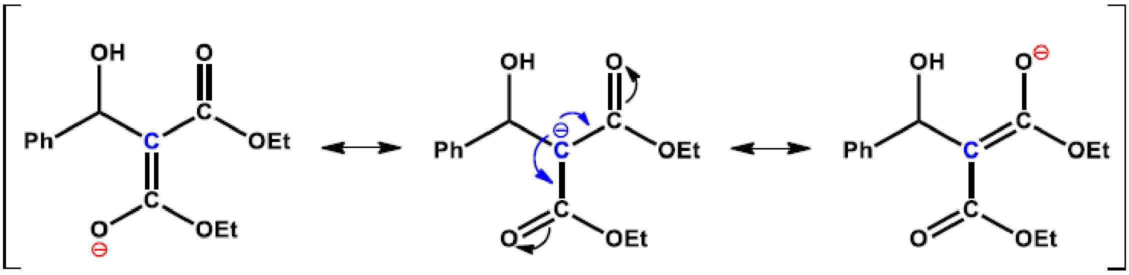
The second step is a fast process in which the leaving group departs from the substrate as a new π bond forms between α and β carbon atoms. At this point, the lone pair of electrons left on the carbanion would move towards the neighboring α-carbon atom resulting in the expulsion of this leaving group while a new π bond forms.

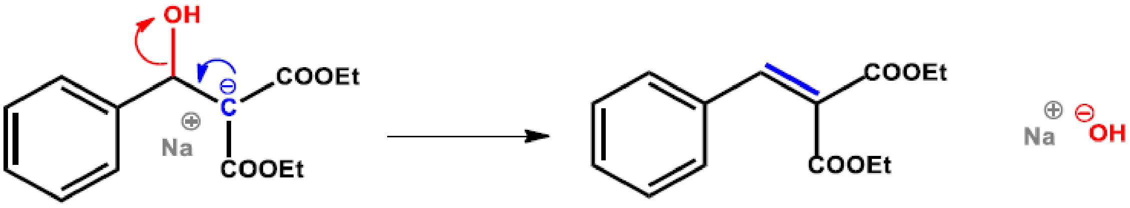


Example

A typical example of an E1cB reaction is the dehydration step of the Knoevenagel condensation reaction.

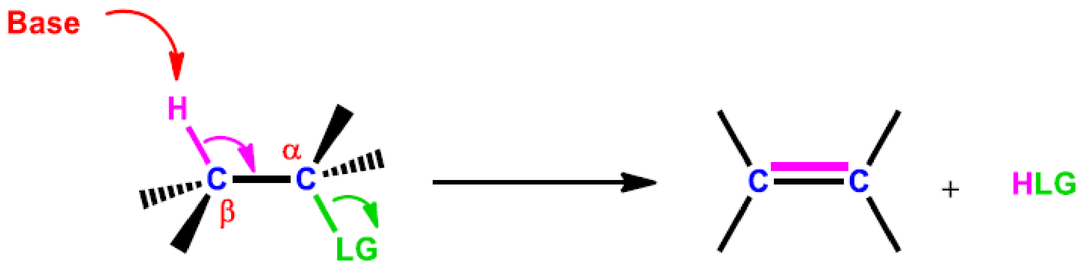




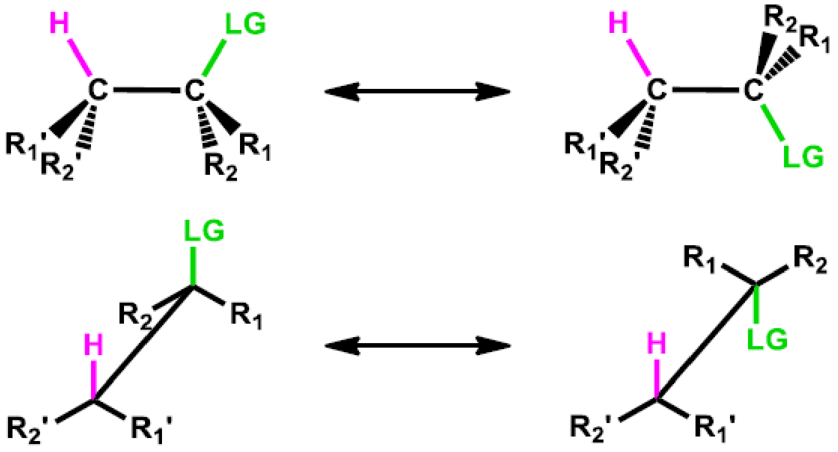


Bimolecular Elimination Reactions E2

E2 reaction is a concerted reaction where both leaving groups leave at the same time. As the base abstracts the hydrogen proton attached to the β carbon atom, the neighboring leaving group gets expelled and a new π bond is formed between α and β carbon atoms.

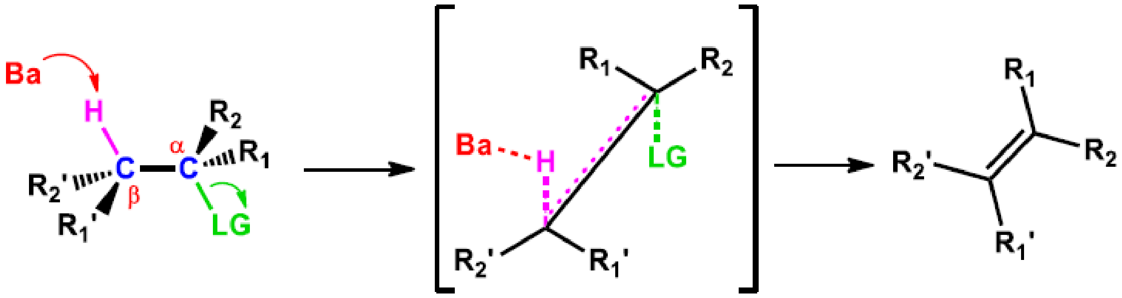


Moreover, for the E2 reaction to occur, the leaving groups must be on the same plane and anti-periplanar to each other. This conformation is necessary for the orbitals to lie in the proper orientation and overlap with each other to form the new π bond. As a result, the substrate must be in the staggered conformation, which has lower energy than the eclipsed conformation.



Eclipsed conformation

Staggered conformation



Antiperiplanar transition state

Kinetics

E2 reaction follows the second-order kinetics. In this reaction, the rate is dependent on both the base and substrate and therefore, increasing the concentration of the base would make the reaction go faster.

Rate=k[Base][Substrate]

Reaction Conditions

Substrate

E2 reaction can occur with all types of substrates "primary, secondary, and tertiary" if they possess a β-hydrogen on anti-position with respect to the leaving group.

Base

Because the base is involved in the rate-determining step in the E2 reaction, the strength and concentration of the base do matter. As a result, the E2 reaction proceeds faster with strong concentrated bases such as sodium methoxide, sodium ethoxide, and potassium t-butoxide.

Solvent

Polar aprotic solvents such as DMSO, and DMF are suitable for E2 reaction since they help stabilize the transition state and do not react with the strong base present in the solution.

Leaving Group

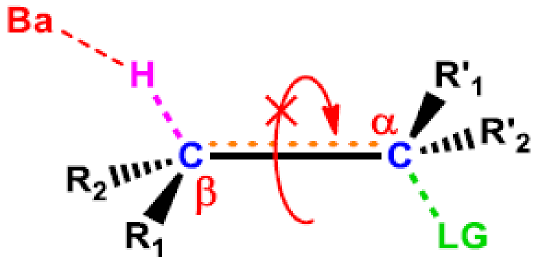
Just like E1 reactions, E2 reactions occur with substrates that possess a good leaving group. However, if the leaving group is too good, the E1 reaction is usually favored.

Regiochemistry and Stereochemistry

E2 elimination is a **regioselective** reaction that favors certain regio-isomers over others. However, unlike the E1 reaction, the E2 reaction is **stereospecific** since it proceeds via a concerted mechanism.

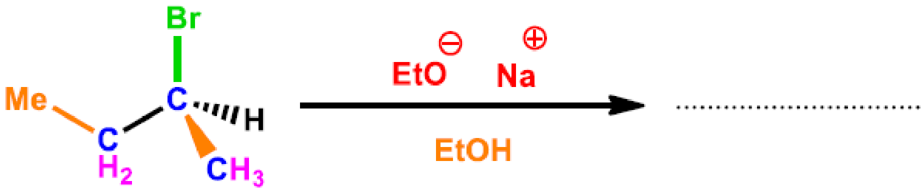
Zaitsev' Rule

With a strong small base, E2 elimination would proceed according to Zaitsev's rule where the most stable products predominate. In this case, the base would preferentially remove the hydrogen proton attached to the most substituted β carbon to produce the most substituted alkene. Nevertheless, it is important to note that the free rotation around the σ bond between α and β carbons is not allowed at the transition state, which makes the reaction **stereospecific** and **regiospecific** (*anti*).

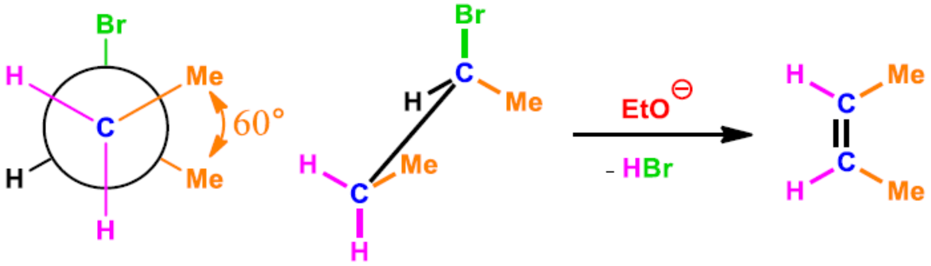


Moreover, the staggered conformation where both leaving groups are anti-periplanar to each other can exist in two different forms; *gauche* conformation and *anti*-conformation when the β carbon has two hydrogen atoms. As a result, the substrate would produce two diastereoisomers *cis* and *trans*.

Example



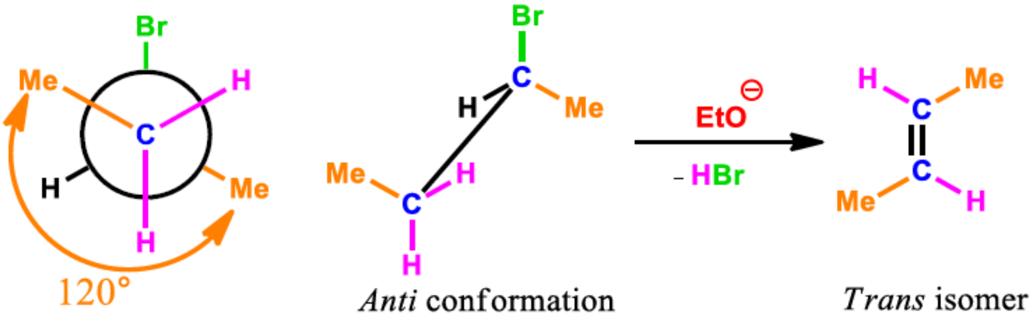
Depending upon the position of the two methyl groups attached to α and β carbons, different diastereoisomers can be obtained as one hydrogen gets removed from the most substituted β carbon. When both methyl groups are aligned according to Gauche conformation, E2 elimination would give a *cis* isomer.



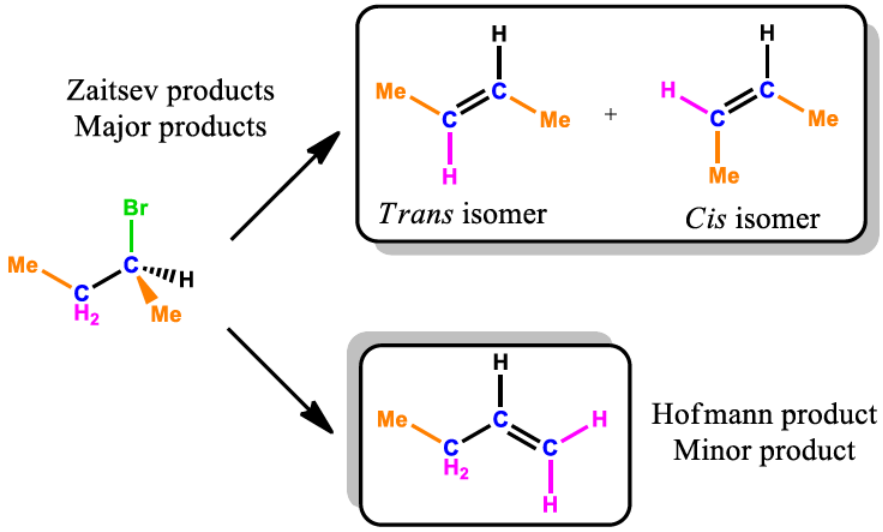
Gauche conformation

Cis isomer

On the other hand, when the angle between the two methyl groups is 120°, the *trans* isomer would be produced.



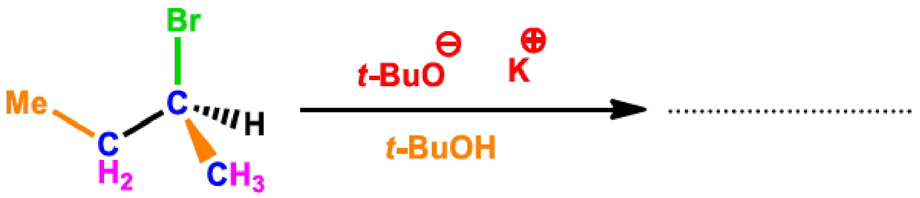
In this case, both diastereoisomers are predominant. However, when the hydrogen proton is abstracted from the least substituted β carbon, a small amount of Hofmann product is obtained.

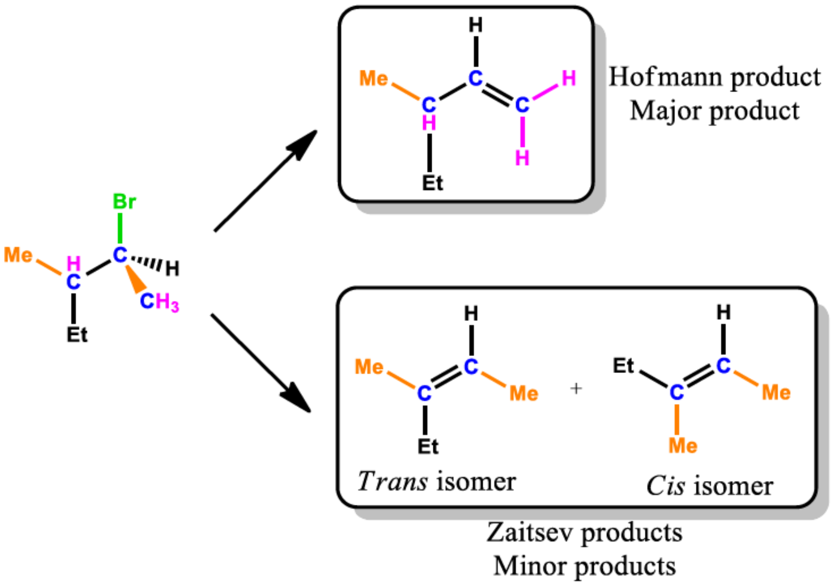


Hofmann's Rule

When a β-elimination reaction is carried with a strong bulky base such as potassium t-butoxide, triethylamine, or 2, 6-lutidine, the steric hindrance of the base would impede it from abstracting a hydrogen atom attached to the most substituted β-carbon. However, it would be easier for the base to abstract a hydrogen atom from the least sterically hindered β carbon. Consequently, the major product would be the least substituted compound and it is called the Hofmann Product.

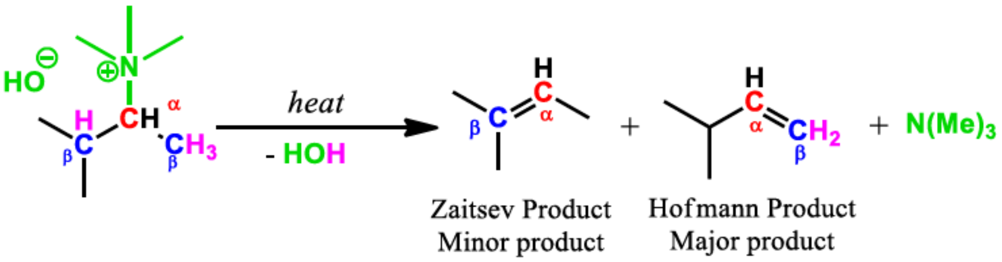
Example





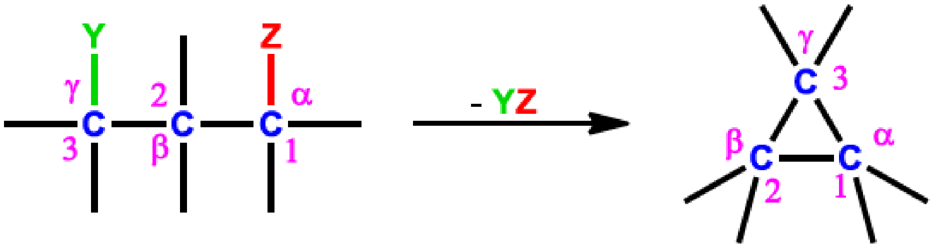
In a similar way, substrates with bulky leaving groups such as quaternary ammonium or sulfonium salts would preferentially produce more Hofmann products than Zaitsev products.

Example



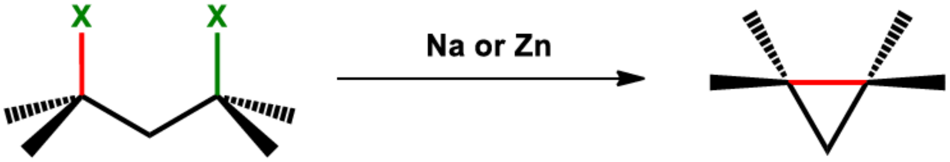
γ- Elimination Reactions

1,3-elimination reactions, also called γ-elimination, is the reaction whereby the two leaving groups are on position 1 and 3 to one another. In this case, the elimination of these groups leads to the formation of three-membered ring compounds.



Freund Reaction

The Freund reaction is a typical γ-elimination reaction that consists in treating 1,3 - dihaloalkanes with sodium to produce cyclopropanes. This reaction can also take place when treating 1,3-dihaloalkanes with zinc dust in a reaction so-called Gustavson reaction.



Mechanism

Initially, metal zinc or sodium inserts into the carbon-halogen bond, which leads to the formation of a negative formal charge on this carbon atom. Later, this carbon would attack the other carbon atom attached to the halogen in position γ resulting in a three-membered ring.