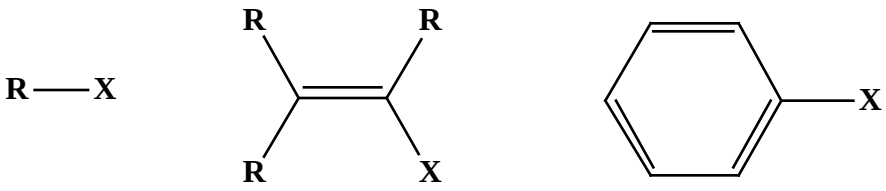
Alkyl Halides
Substrates for Nucleophilic Substitution & Elimination

Organohalogen Types



Alkyl Halide Vinyl Halide Aryl Halide. Ar-X

Hybridizations: C sp^3 for alkyl halides and C sp^2 for the others. Chlorine get's the sp^3 hybridization if we assume that the lone pairs also are hybridized.

Nomenclature

Lots of trivialnames (e.g. chloroform). IUPAC nomenclature can be applied as discussed earlier. Use the "o" after the halogen just so it is easier to pronounce.

Example 1: Iodomethane or methyl iodide

Example 2: Fluorocyclohexane or cyclohexyl fluoride

Example 3: 1-Iodo-2-methylpropane

Example 4: (1-Iodoethyl)-cyclooctane

Geminal and Vicinal Dihalides

Geminal: 1,1-dihalo. Vicinal: 1,2-dihalo.

Alkylhalides and Degree of C-Substitution

In the reactions of halides, it matters a lot whether the X is attached to a methyl group (H_3C-), to a methylene group (-CH_2-), to a methyne group (-CH<), or to C without any Hs attached. To facilitate the discussion below, we use these terms. The C that carries the X is the "head" C ("C heads")

Carbon Type	Short	# of C attached	# of H attached
Methyl carbon		0 C	3 Hs
Primary carbon	1° C	1 C	2 Hs
Secondary carbon	2° C	2 C	1 H
Tertiary carbon	3° C	3 C	0 H

Uses - Past and Present

Solvents

carbon tetrachloride (dry cleaning, carcinogenic), **1,1,1-trichloroethane** (replaces tetra), **methylene chloride** (used to be used to decaffeinate coffee until found to be a carcinogen), **chloroform** (cleaning solvents, carcinogenic)

Anesthetics

$HCCl_3$, chloroform, historically significant.
F_3C-CClBrH, halothane, modern use.
Ethyl chloride, local anesthetic, low boiling point (12˚C) leads to evaporation and cooling to enhance the numbing effect.

Refrigerants

Ammonia "refrigerant" in cooling systems were replaced by chlorofluorohydrocarbons, **CFC**.
CCl_2F_2, Freon 12, one of the main sources of chlorine in the atmosphere, responsible for ozone hole.
Now in use are **HCFCs**, compounds that contain CH bonds.
$HCClF_2$, Freon 22; F_3C-CCl_2H, HCFC-123

Insecticides, Pesticides

1939, DDT, di(*para*-chlorophenyl)-trichloroethane
1972, banned by the EPA. DDT accumulates in fatty tissue.
Currently used insecticides: Lindane, Kepone, Aldrin, Chlordane. See visualization center to Chapter 6.

Physical Properties

Dipole Moments. The C-X bond moments depend on the EN difference (F > Cl > Br > I) and on the bond length (CF < CCl < CBr < CI). For the methyl halides the values are given in the table. CH_3F deviates because of the short bond.

	Me-F	Me-Cl	Me-Br	Me-I
Length (Å)	1.385	1.784	1.929	2.139
Dipole (D)	1.82	1.94	1.79	1.64
Strength (kcal/mol)	110	85	71	57

Dipole-dipole interactions. No H-bonds. Heavier than water. Do not mix with water (polar, but not very polar).

Except for methyl iodide, **methyl halides** are gases at room temperature**. Halides with several halogens** are liquids.

CH_3F	CH_3Cl	CH_3Br	CH_3I
-78	-24	4	42

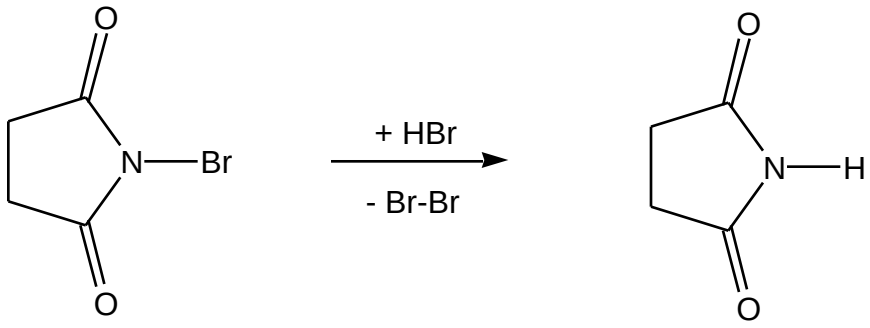
CH_3Cl	CH_2Cl_2	$CHCl_3$	CCl_4
-24	40	61	77

Preparation of Alkylhalides

(a) Radical Halogenations (as discussed)

(b) Allylic Bromination with N-Bromosuccinimide (NBS)

NBS reacts with HBr to give Br_2 in low concentrations. Bromine at this concentration does not add to double bonds. Hence with NBS **allylic** radical brominations are possible. The allylic bromination generates one HBr for every consumed Br_2 molecule. This HBr reacts again with NBS to generate another Br_2. …



(c) From Alcohols

R-OH + HX -(in ether)-> R-X + H_2O

Elimination (alkene formation) competes. For tertiary alcohols this is fast. For primary and secondary alcohols, we use (PBr_3 / ether / 35˚C) or ($SOCl_2$ / pyridine) instead of HX. Details in the discussion of the chemistry of alcohols.

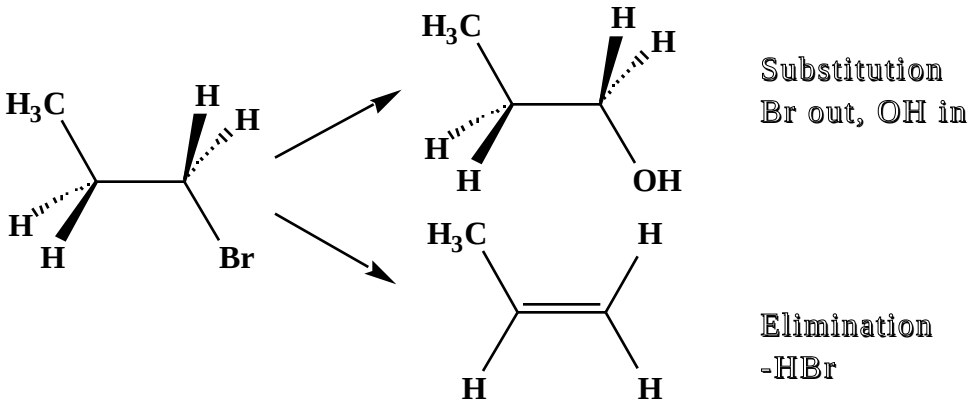
(d) From Alkenes and Alkynes

Addition of halogens or of HX to alkenes and alkynes. To be discussed in later chapters.

Reactions of Alkyl Halides - Substitution & Elimination

The Big Picture

We'll be looking at reaction between **nucleophiles** (usually reagents with lone pairs and negative charge; e.g. OH^-) and alkyl halides. Two reaction types dominate. **Substitution** and **elimination**. Sometimes one occurs, sometimes the other, and sometimes they compete. We'll study each case and try to figure **when what** happens and **why**.



Substitution Reaction. A **leaving group** X is ejected as a **nucleofug** and replaced by an incoming **nucleophile** Y.

Elimination Reaction. A leaving group X and a proton are eliminated. When the H comes from the *beta*-carbon, then we talk about *beta*-eliminations. *Beta*-eliminations also are called 1,2-eliminations.

Nucleophiles are our reagents. Nucleophiles are "nucleus lovers", that is they are "attracted" to reaction centers with positive charge. The head-C in alkyl halides are positively polarized. Obviously, what likes to get to a positive charge needs to be negative (anions) or at least have some lone electrons or both (most usually).
Example: Water and hydroxide anion.

Electrophiles are the opposite ("electron lovers"). Electron deficient often cationic molecules.
Example: A proton.

Nucleophilicity and Basicity. Negative ions are thus nucleophiles, reagents that react with positively polarized carbons. But wait, negative ions also are basic because they are the conjugate bases of acids. As bases, these anions would remove protons (elimination) and as nucleophiles they would replace the X (substitution). So, we have a situation where a given reagent could do either type of reaction and it's hard to say which is going to happen. We have no way to tell *a priori*. Basicity and nucleophilicity are not related in a straightforward manner. We'll get "a feel" for this as we go along. Then later we look at this question again.

Nucleophilic Substitution Reactions

Two basic mechanisms for nucleophilic substitution, S_N.
The classical examples are
(a) the reaction of hydroxide with bromoethane and
(b) the reaction of hydroxide with *tert* butylchloride.

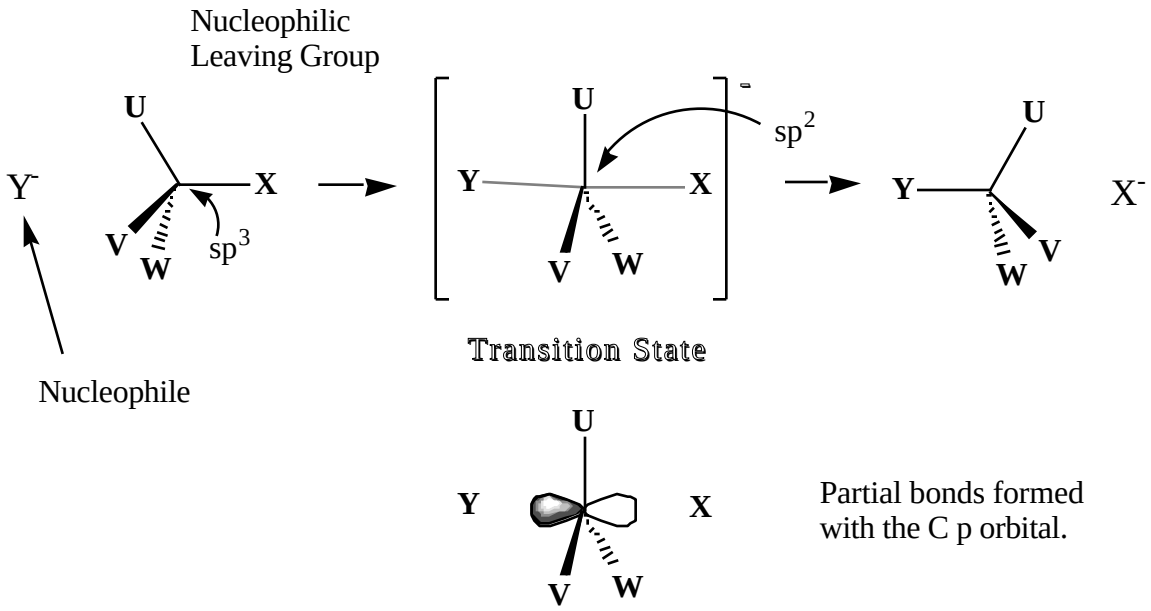
Example (a) proceeds in one step: Hydroxide comes in and bromine is replaced. There are no intermediates. Two molecules take part in this step: **S_N2**.

Example (b) proceeds in two steps: Bromine leaves and a cation is formed. That intermediate reacts with hydroxide. The second step will happen fast. In the first step - the slow step - only one molecule is involved: **S_N1**.

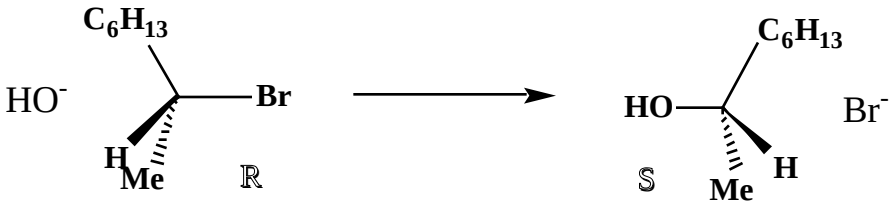
We'll look at these two types of mechanism now in detail. We ask questions like this:
(a) What products and side products?
(b) Are there intermediates? How many steps?
(c) What are the energies of the intermediates.
(d) What are the transition states like?
(e) What are the energies of the transition states.
(f) What steps are fast, which one is slow?
(g) Stereochemistry? Isomers possible?
(h) *Can we control the outcome?* (The name of the game!)

The S_N2 Reaction

General Mechanism

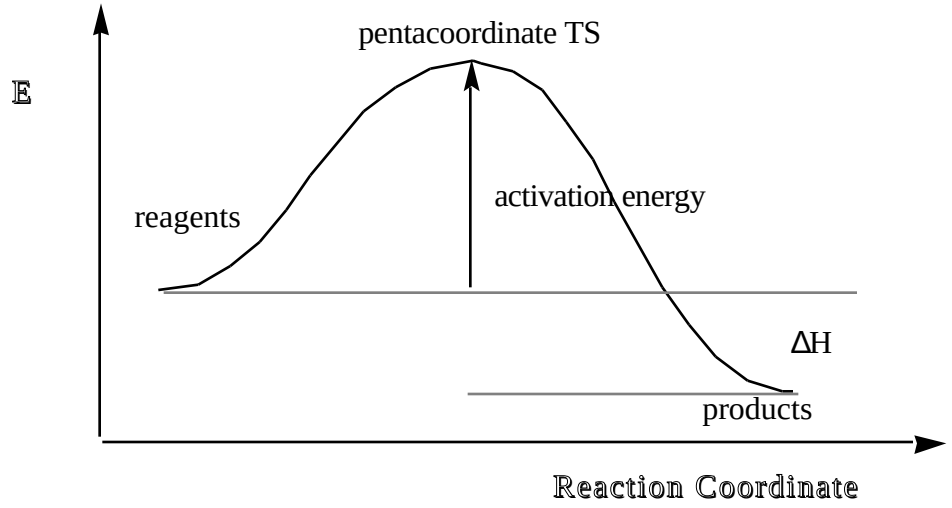


Specific Example



Note the configuration changes! Stereospecific reaction.
Walden inversion.

Energy Profile

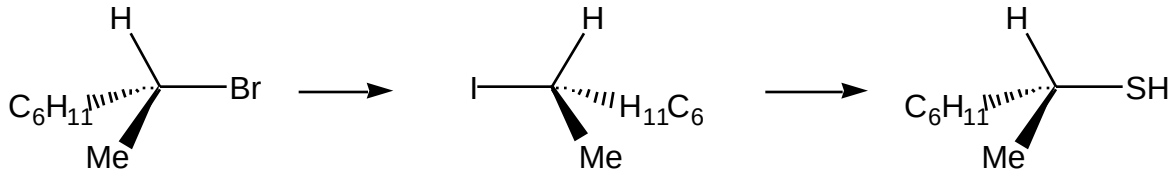


Inversion of configuration. The configuration of the chiral carbon in the specific example is inverted. This **Walden inversion** may or may not show up in the R/S system of nomenclature. Usually the leaving group and X will both have the highest priority; then *R* turns into *S* and *vice versa*. If however, a hydroxide would replace a chlorine and there was another N, F or such a substituent in the reagent, then there might not be a change in *R/S* despite the Walden inversion.

The S_N2 reaction is **stereospecific**. A given stereoisomer will result in a product with a defined configuration as well (usually the opposite). In particular, the product will **not** be a racemic mixture.

How to Achieve Retention of Configuration

Do the inversion twice! Consider the reaction of (*R*)-2-bromooctane with (a) iodide and subsequently with (b) hydrogensulfide anion. Both reactions proceed with complete inversion and the overall result is retention of configuration. Consider for example the reaction of (*R*)-2-bromooctane.



Reaction Kinetics

Bimolecular - The real reason for the "2". Bimolecular reactions in general are reactions in which two molecules participate in the slow step of the reaction. Here we have just one step, it is obviously the slow step, and it involves the nucleophile and the halide.

Reaction Order. As it turns out, the rate of reaction is proportional to the concentration of each of the participants in the slow step. (This does not need to be so.) Here:

$$S_N2 \text{ rate} = k\ [\text{nuc}]^1\ [\text{halide}]^1$$

k is the reaction constant and its units are $s^{-1}\ l\ mol^{-1}$.
The units of the rate (conc. change per time) are $mol\ l^{-1}\ s^{-1}$.
Example: 0.01 molar sodium azide reacts with 0.01 molar iodomethane in MeOH at 0˚C with a rate of $3 \cdot 10^{-10}\ mol\ l^{-1}\ s^{-1}$.
Yes, negative 10 in the exponent. $k = 3 \cdot 10^{-6}\ mol^{-1}\ l\ s^{-1}$.

Note the exponent "1" (which could be omitted). The exponents indicate the **order** by which the reagents "enter into the rate equation". Well, the order is one for each in this case. The **reaction order** is the sum of all these exponents. Here, it is 2. We have an example of **second-order kinetics**. For now, let's just use these terms to describe the reactions. The value of these definitions will become clear later.

Factors Affecting the Activation Barrier of the S_N2 Reaction

The rate is of course related to the activation energy. The lower the activation barrier, the higher the rate. So, the question is what affects the activation barrier or, in other words, what affects the energies of the substrate and of the transition state?

(1) C-X Head Carbon Type

Turns out that methyl halides react much faster than the primary halides under the same conditions. For reagents with primary C-X functions, there also are some small variations depending on the chain lengths. To get an idea of the magnitude, look at these numbers for the S_N2 reactions of halides.

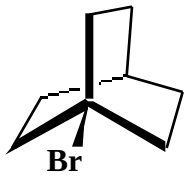
Compound	Relative Rate
$H\text{-}CH_2\text{-}X$	30
$H_3C\text{-}CH_2\text{-}X$	1
$H_3C\text{-}(CH_2)_2\text{-}X$	0.4
$H_3C\text{-}(CH_2)_3\text{-}X$	0.4

(2) Steric Effects

Change in C hybridization from sp^3 to sp^2. The substituents at C are more removed from each other (that is good) but they come closer to the leaving group and in addition they will have repulsive interactions with the nucleophile. The transition state is pretty "crowded" as we say. Bulky groups don't like that, rates go down. Tertiary halides are so much slowed down, that the S_N2 reaction essentially does not occur. Relative rates are based on the reaction of the neo-pentyl bromide (tBu-CH_2-Br).

Substrate	relative rate
methyl bromide	3,000,000
ethyl bromide (prim.)	100,000
iso-propyl bromide (sec.)	2,500
neo-pentyl bromide (prim.)	1.0
t-butyl bromide (tert.)	<< 1.0

Steric effects also are key for the lack of reactivity of the bridgehead bromide shown. This molecule cannot undergo S_N2 chemistry because the Walden inversion is not possible; attack from the back-side is impossible.



Show transparencies on attack and on TS crowding.

(3) Nucleophile Strength

The way to determine the **nucleophilicity** is simply to do one type of reaction with all kinds of nucleophiles and compare the rates of reactions. The simplest system is the reaction of nucleophiles with methyl bromide or methyl chloride.

$Me\text{-}Br + H_2N^- \rightarrow Me\text{-}NH_2 + Br^-$	fast
$Me\text{-}Br + H_3N \rightarrow Me\text{-}NH_3^+ + Br^-$	slow
$Me\text{-}Br + HO^- \rightarrow Me\text{-}OH + Br^-$	fast
$Me\text{-}Br + H_2O \rightarrow Me\text{-}OH_2^+ + Br^-$	slow
$Me\text{-}Br + H_3N \rightarrow Me\text{-}NH_3^+ + Br^-$	fast
$Me\text{-}Br + H_2O \rightarrow Me\text{-}OH_2^+ + Br^-$	slow
$Me\text{-}Br + H_2N^- \rightarrow Me\text{-}NH_2 + Br^-$	fast
$Me\text{-}Br + HO^- \rightarrow Me\text{-}OH + Br^-$	slow

Remember these trends (which are related to electronegativity):
(A) Nucleophilicity parallels basicity (but is not always equal to it); e.g. $HS^- >> HO^-$.
(B) Nucleophilicity increases in going down a column, e.g iodide > bromide > chloride.
(C) Nucleophilicity decreases within a period

Show table 6-3 on transparency.
Show figure on size effect on LUMO attack.

(4) Leaving Group Ability

The leaving group will almost always be an anion. Everything that stabilizes the anion makes the anion a better leaving group.

Anions always suffer from **electron-electron repulsion** and this destabilizing effect is related to size. The larger the anion the better. For example, I^- is a very good leaving group and F^- is the worst leaving group. (Yes, iodide is the best nucleophile and also the best leaving group.)

The best leaving groups are "groups" where the anionic character is distributed over several atoms. Examples include

Alkylsulfates $RO\text{-}SO_2\text{-}O^-$

Methanesulfonate ion (mesylate) $Me\text{-}SO_2\text{-}O^-$

Trifluoromethanesulfonate ion (triflate) $CF_3\text{-}SO_2\text{-}O^-$

4-Methylbenzenesulfonate ion (tosylate) $Me\text{-}C_6H_4\text{-}SO_2\text{-}O^-$

(5.1) Solvent Effects on Nucleophile Strength

Protic solvents can form H-bonds with nucleophiles and they make it harder for the nucleophile to react. Aprotic solvents do not form such H-bonds and the nucleophiles are therefore more available for attack.

Important aprotic and polar solvents are:

Acetonitrile
Dimethylformamide, DMF
Acetone

(5.2) Solvent Effects on Activation Barrier

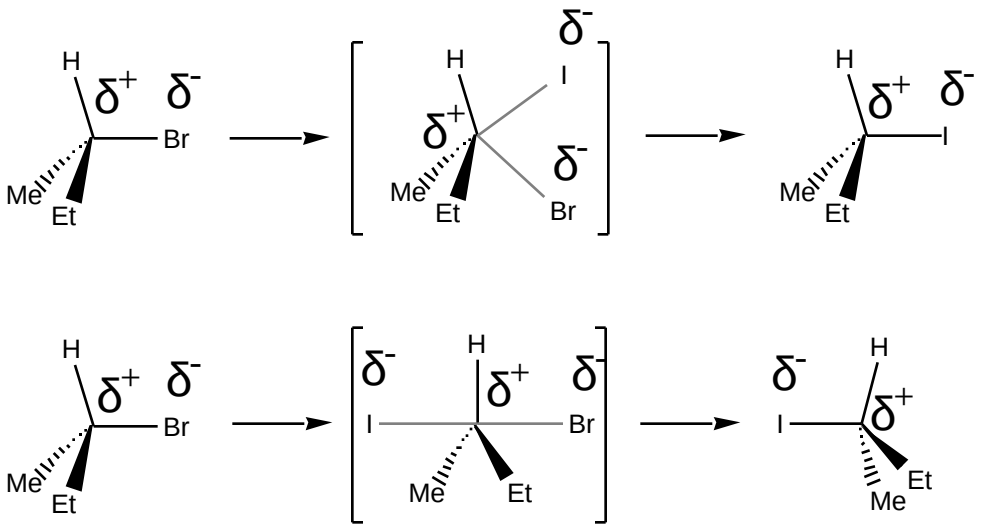
Substrates: Anionic nucleophile and neutral substrate.
TS: Minus charge **distributed** over nucleophile and nucleofug!
Product: Anionic nucleofug and neutral substrate.
Very polar solvents stabilize substrate and product more than TS; the **activation barrier increases** with solvent polarity.

(6) Steric Effects on Nucleophilicity

Bulkiness hinders nucleophilicity (the power to approach a positively polarized carbon) while it has hardly any effect on basicity (the poer to attract protons).
Tert.-butoxide: good base, poor nucleophile. No S_N2.
Ethoxide: lesser base, better nucleophile. Good S_N2.

Backside versus Frontside The S_N2 Reaction

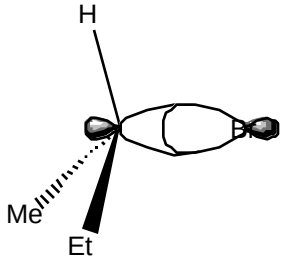
So far, we discussed the backside attack with the Walden inversion. In principle, there also is the possibility for frontside attack with retention of configuration.



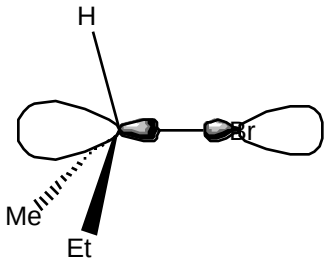
The stereochemical outcome is the only source of information that can tell us about which of the two paths is taken. Since most S_N reactions do go with inversion, the S_N2 reaction is generally considered as the favorable option.

Backside versus Frontside The S_N2 Reaction
Where is the LUMO?

The antibonding MO of the C-X bond is oriented to favor backside attack.



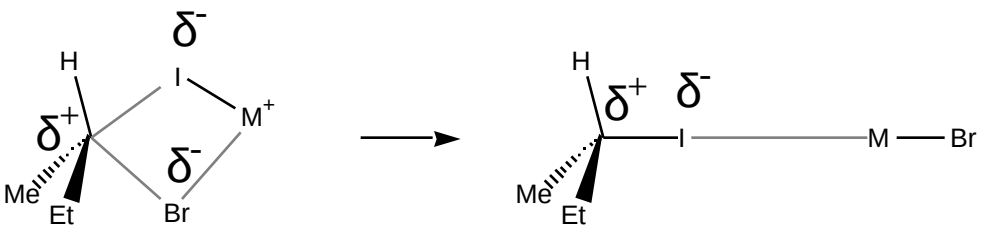
Occupied bonding MO



Empty anti-bonding MO of the C-X bond. The MO is the acceptor for the nucleophiles electrons.

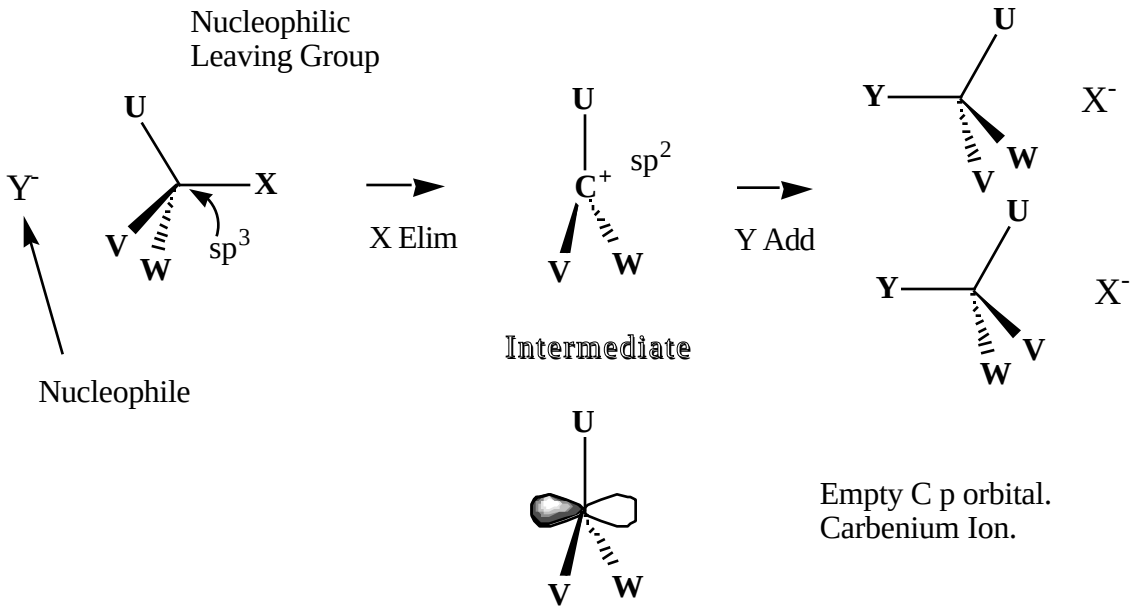
The Frontside S_N2 Reaction

The frontside attack can become possible in cases where the attacking nucleophile reacts as an **ion pair**, that is, the attacking nucleophile carries a cation around. In such a case, the frontside attack might become farvored because the cation can interact with the leaving group. For the ion pair to react via the backside attack, one would have to overcome the energy associated with generating separated ions as the cation provided by the reagent and the nucleophilic leaving groups are far apart from each other.

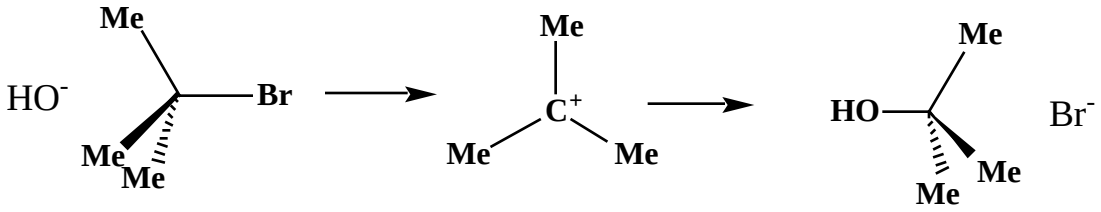


The S_N1 Reaction

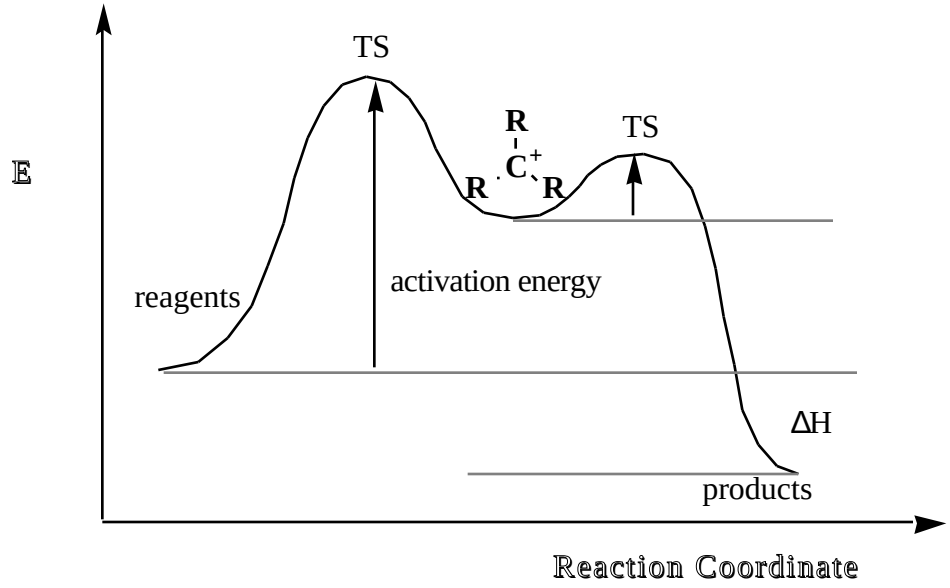
General Mechanism



Specific Example



Energy Profile



Stereochemistry

The important thing here is that the intermediate is **planar**. Consequently, the addition of the NUC can occur from either side **with equal probability**. Hence, if there are three different substituents on the carbocation, then the fourth one can give either *S* or *R* - and it will. **Racemization!** No matter what configuration you start out with, you loose it! This is one of the reasons why we would like to be able to avoid S_N1 mechanisms as much as possible. (Others below.)
(Show transparency here)

Molecularity of the Reaction

This is a case of a *monomolecular* or *unimolecular* reaction -- just one molecule is involved in the slow step, the dissociation of the C-X bond.

Reaction Rate and Reaction Order

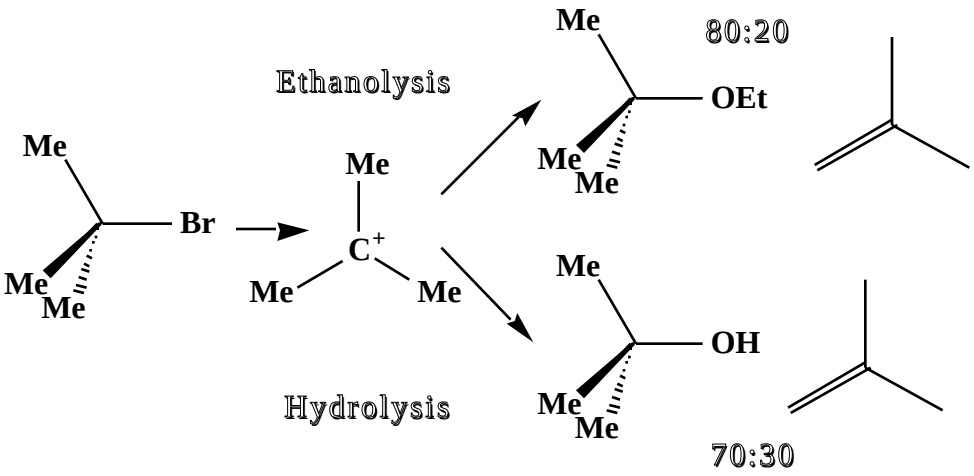
The rate thus just depends on the concentration of the halide, first order. The $[Nuc]^0$ does not matter!

$$S_N1 \text{ rate} = k\,[\text{halide}]^1$$

Solvolysis

Reactions in which the solvent also acts as the reagent are called **solvolysis** reactions. The **hydrolysis** reaction is the special case in which water is the solvent. The reaction with ethanol in the solvent ethanol would be called **ethanolysis**.

Let's look at the ethanolysis and the hydrolysis of *tert* butylbromide. The bromide is 3° and S_N1 chemistry is indicated. There are three things to learn here: (1) There are side products and (2) the ratio of product/side products is not the same for the two reactions and (3) there might be additional fast steps involved. This is what happens:



Proton elimination competes. Water is a better Nuc than ethanol and captures more cations. The nucleophile in both cases are neutral molecules. Once the O adds, it becomes positively charged as it shares its e-pair with the C. Proton loss occurs fast. (Homework: Draw it out!)

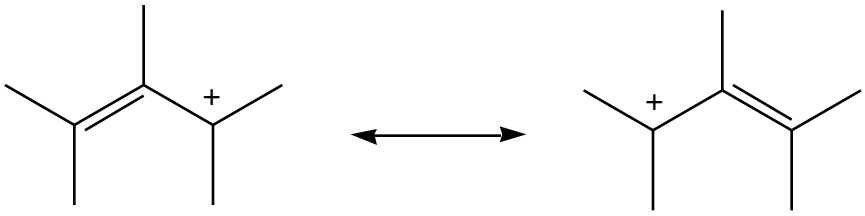
Relative Reactivities in S_N1

The rules: 3° halides react *via* S_N1
2° halides sometimes do S_N1 (also S_N2)
1° halides never do S_N1.

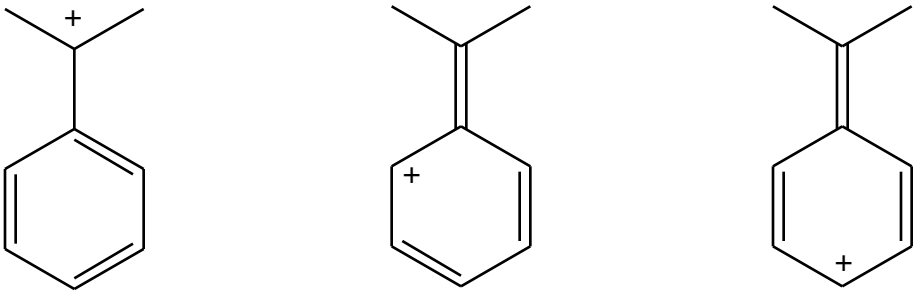
The S_N2 reaction requires a strong nucleophile or it won't go. Typical solvolysis conditions do **not** have strong nucleophiles (neutral solvent molecules). Solvolysis are mostly S_N1 and they go only easily with 3° halides because these can form relatively stable carbenium ions.

Carbenium Ion Stabilization

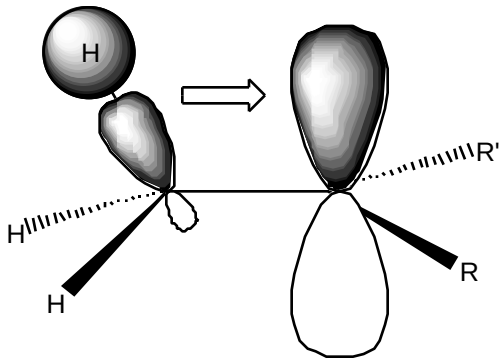
(a) Vinyl substitution giving allyl cations (Conjugation)



(b) Phenyl substitution giving benzyl cations (Conjugation)



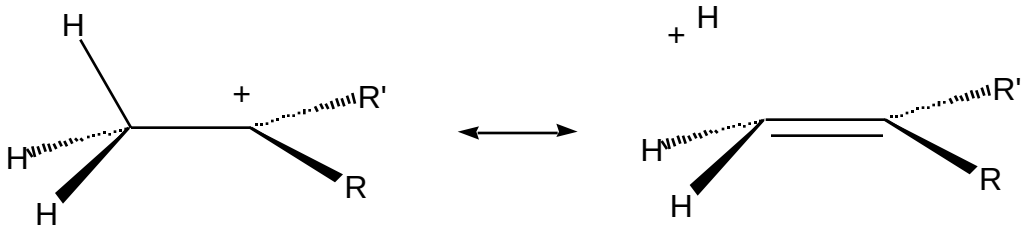
(c) Multiple alkyl substitution (Hyperconjugation)



Electron donation from the sigma bond into the empty p-AO of the carbenium ion center. This sort of intercation requires alignment of the C-H bond and the p-AO in the same plane.

C-H bond donate better than C-C bonds. That is, trimethyl-methyl cation is more stable than tri-tert.-butyl-methylcation.

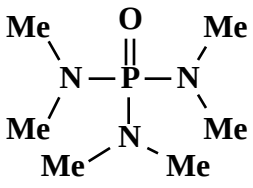
Representation of Hyperconjugation using Resonance Forms:

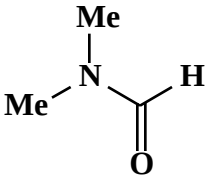


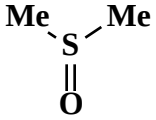
Solvent Effects

Polar solvents facilitate dissociation: **Two ions are generated from a neutral species!** The polar solvent stabilizes the ions much more than it stabilizes the polar substrates and products. The dielectric constant estimate solvent polarity. Let's look at some important solvents and their DCs.

APROTIC SOLVENTS	DC	PROTIC SOLVENTS	DC
Hexane	2	Acetic Acid	6
Benzene	2	Et-OH	24
Diethyl ether	4.3	Me-OH	34
Chloroform	5	Formic Acid, HCOOH	58
HMPA, Hexamethyl-phosphoramide	30	Water	80
Dimethylformamide DMF	38		
Dimethyl sulfoxide DMSO	48		





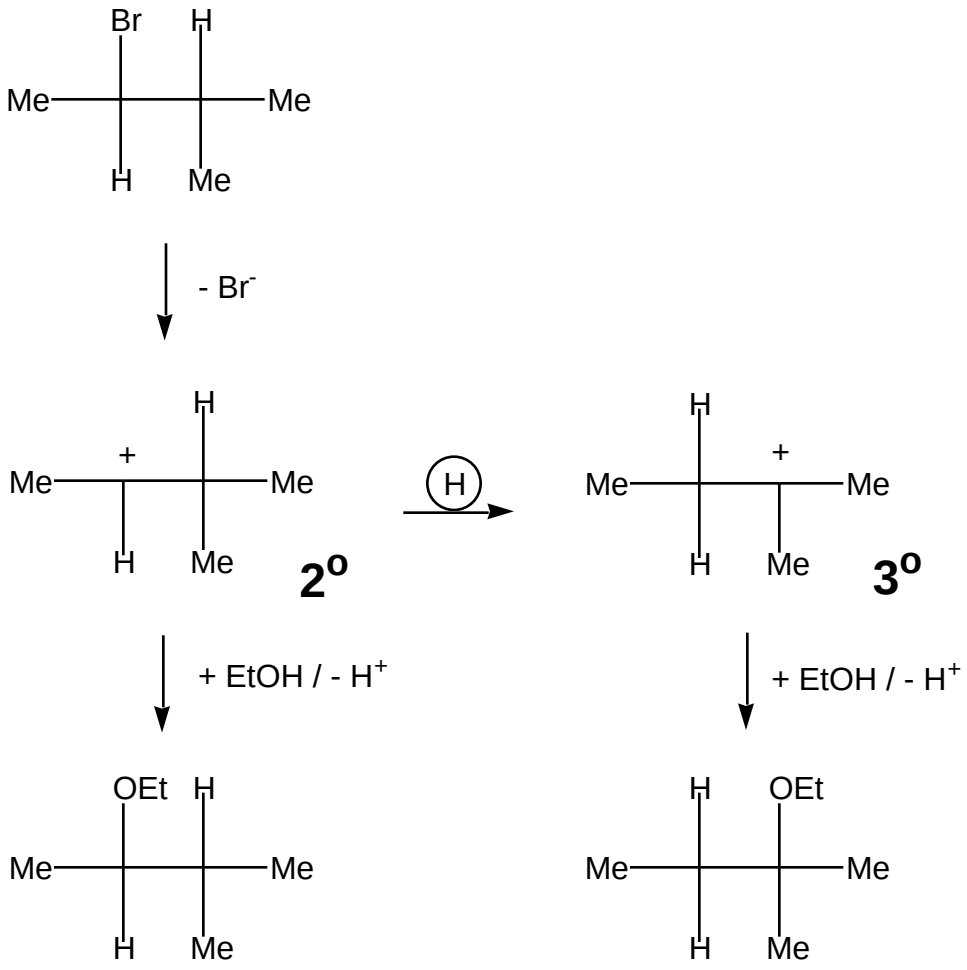


Rearrangements in S_N1 Reactions: 1,2-Shifts

Purpose: Generate a carbenium ion that is more stabilized.

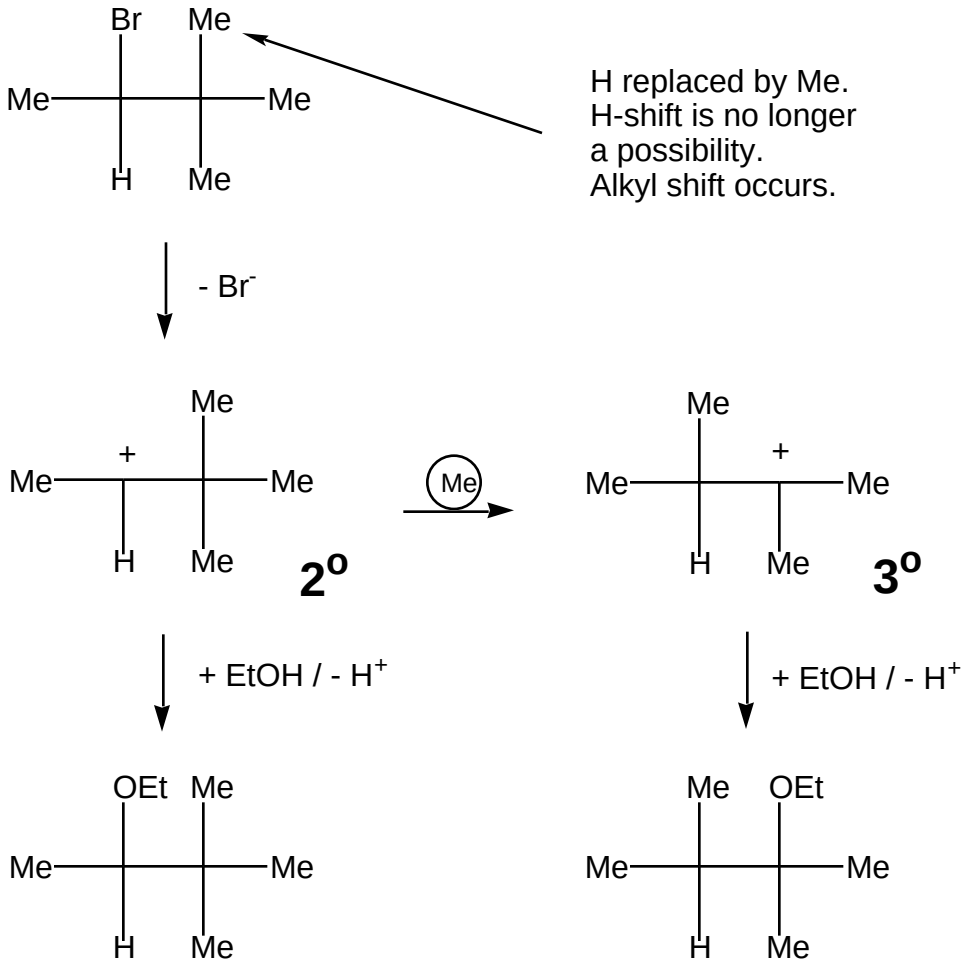
1. Hydrogen Shifts

The reaction of 2-bromo-3-methylbutane with ethanol give two products: The expected 2-ethoxy-3-methylbutane and the rearranged 2-ethoxy-2-metylbutane.



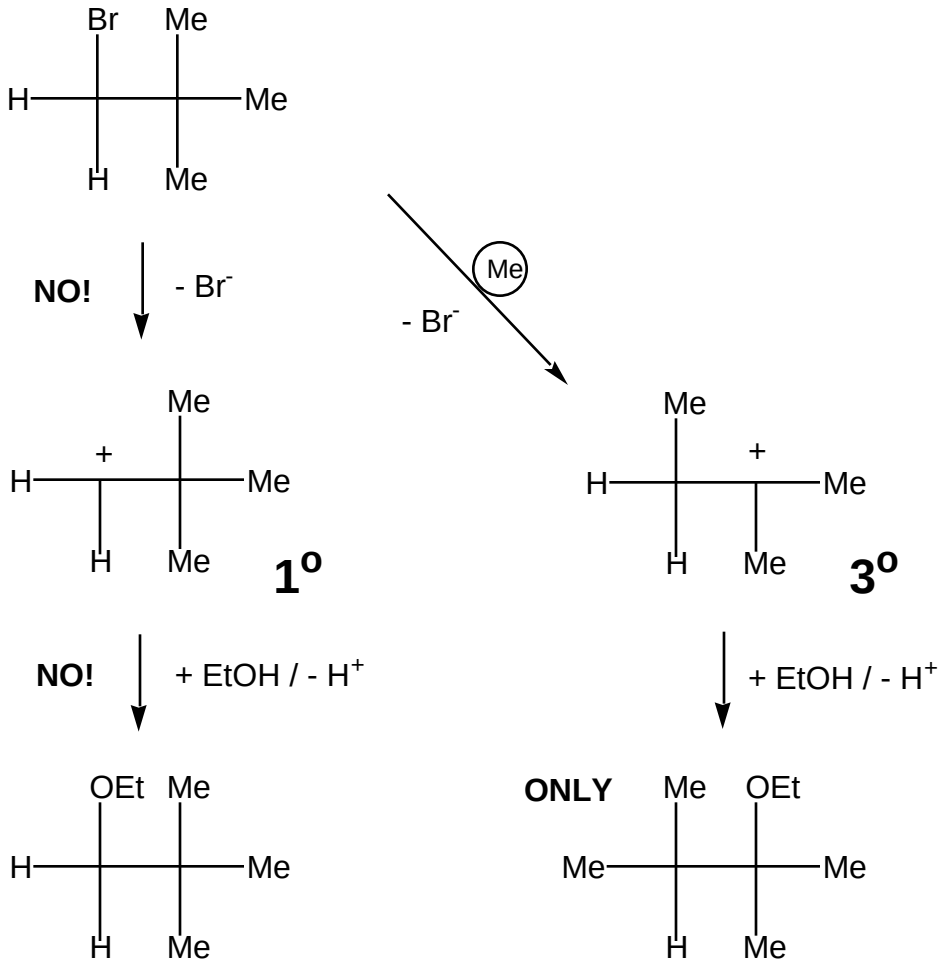
2. Alkyl Shifts - Methyl Shifts

A very similar situation, except that H-shift is no longer an option. Now an alkyl shift is used to generate the more stable cation. If an alkyl group migrates, a **skeletal rearrangement** occurs.



3. Alkyl Shifts in Concert with Ionization

This quite interesting and something to keep in mind. There are situations where primary alkyl halides may undergo S_N1 reaction! In situations where an alkyl shift can occur during the ionization, the primary carbenium is bypassed and the more stable rearranged carbenium ion is formed right away.



Elimination Reactions

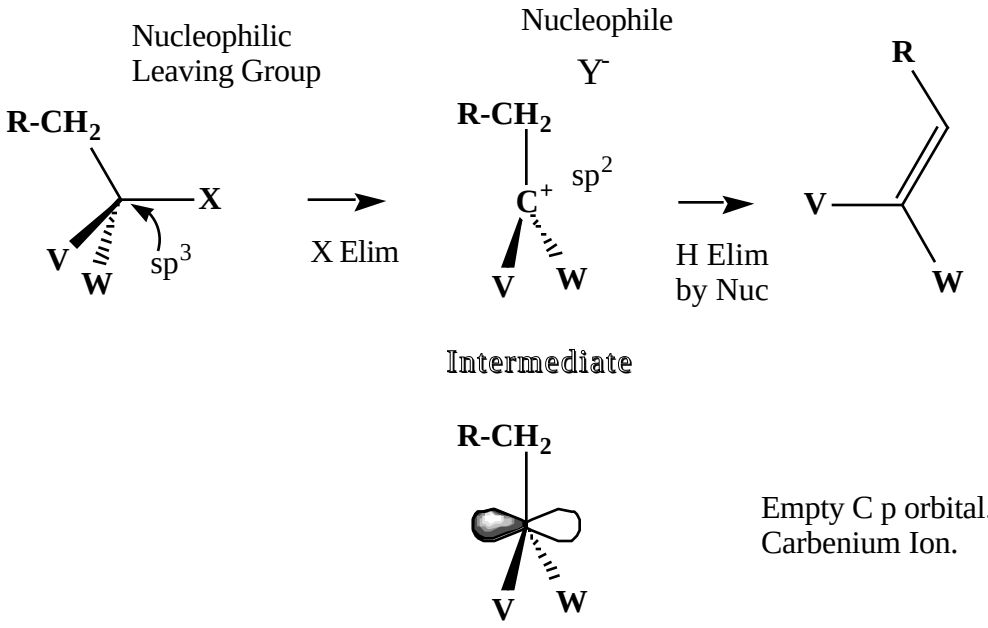
Halides and other functionalized alkanes can form alkenes by elimination of HX. The **timing** of the reaction either involves

E2: simultaneous elimination of X and H or
E1: first X, then H
E1cb: first H, then X.

E1cb stands for “E1 cum base”. Let’s look at each in some detail. During the entire discussion always look for similarities and differences compared to nucleophilic substitutions!

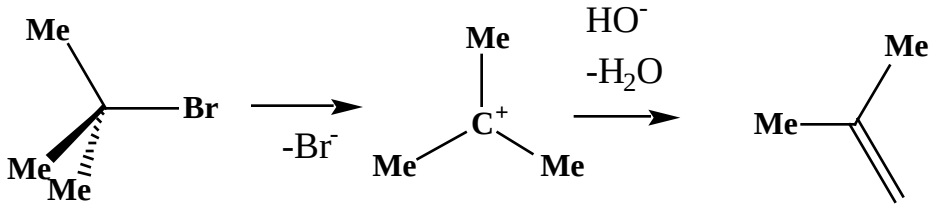
The E_1 Reaction

General Mechanism



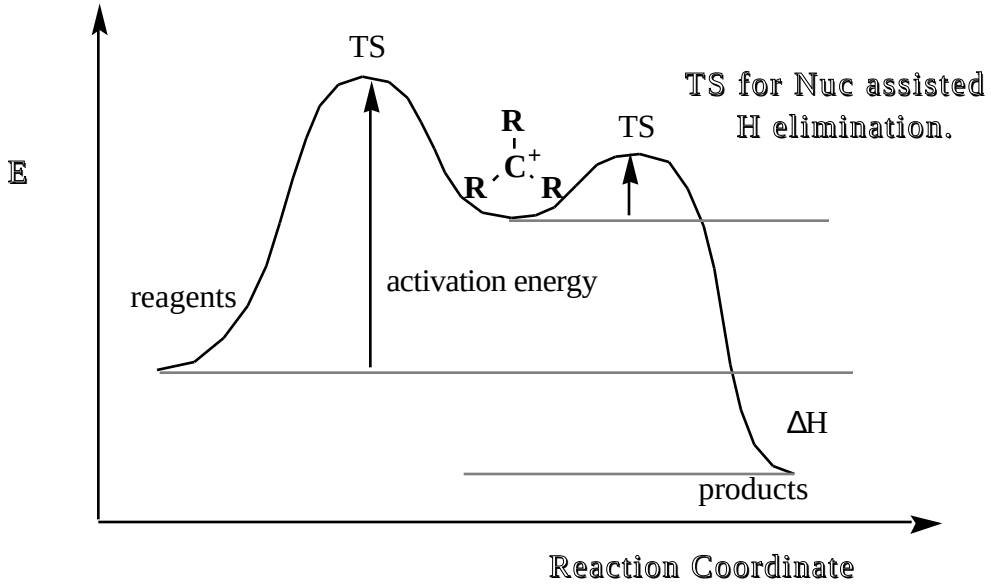
Note the similarity with the S_N1 mechanism. The first step is the same; the differences is with the reaction of the carbenium ion. **Proton** elimination.

Specific Example



Energy Profile

This is qualitatively the same as for the S_N1 reaction. The only difference is that the second TS now is the TS for H-elimination (instead of Nuc-addition) and that the product is the olefine.



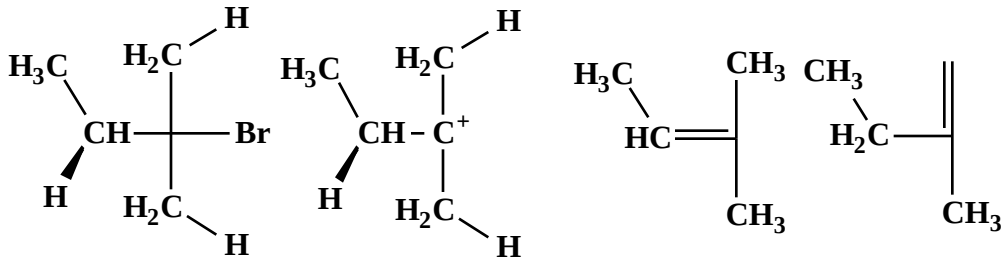
Regiochemistry and Stereochemistry

We don't need to worry about stereoisomers. The original configuration is lost because of the symmetric intermediate and the H loss does not generate chiral carbons either.

We do have to worry about **regiochemistry**. Regiochemistry refers to the **specific region** where the action is. There might be a choice regarding which "β-H" is eliminated.

Example: 1,1-dimethyl-1-bromo-propane

Two olefines can be formed depending as to whether the methylene H or the methyl H is eliminated.



Which one is going to be produced more? A question of Statistics and Stability.

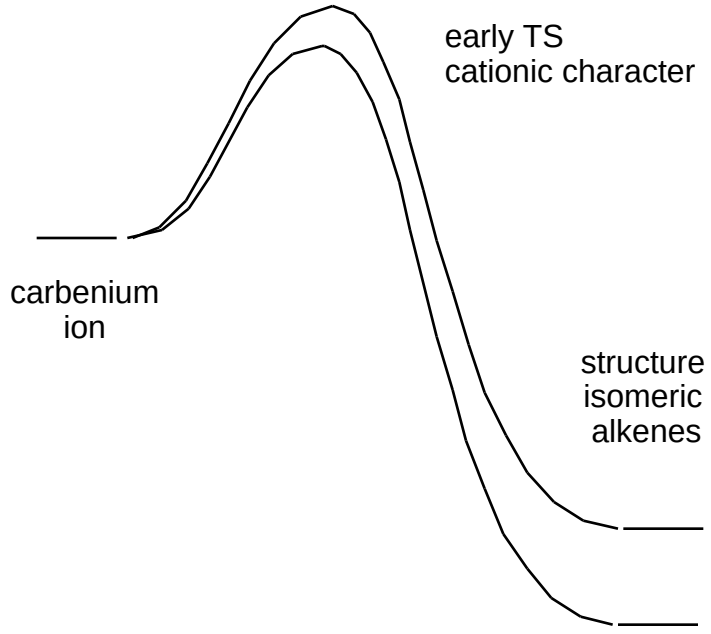
Statistics: There are 6 methyl Hs and only two methylene Hs. Methyl H elimination is statistically more likely.

Stability: The stability of the product is more important.

The **Saytzeff** rule: The more alkyl substituted double bond is formed!

Saytzeff Rule

This rule can be understood by considering the energy profiles of the two possible reactions. We'll have to look at the **second** TS, the TS for the faster reaction step. This TS is lower in energy for that reaction that leads to the more stable product. Note that the TS is early and still has some carbenium ion character. We already learned that carbenium ions are more stable if there are alkyl substituents attached. So, the alkyl groups stabilize both the transition state structures and the products. What really matters is the relative energy of the TSs (!) but because the same stabilization mechanism operates for them and for the products, we can simply look at the products when we decide about the regiochemistry.

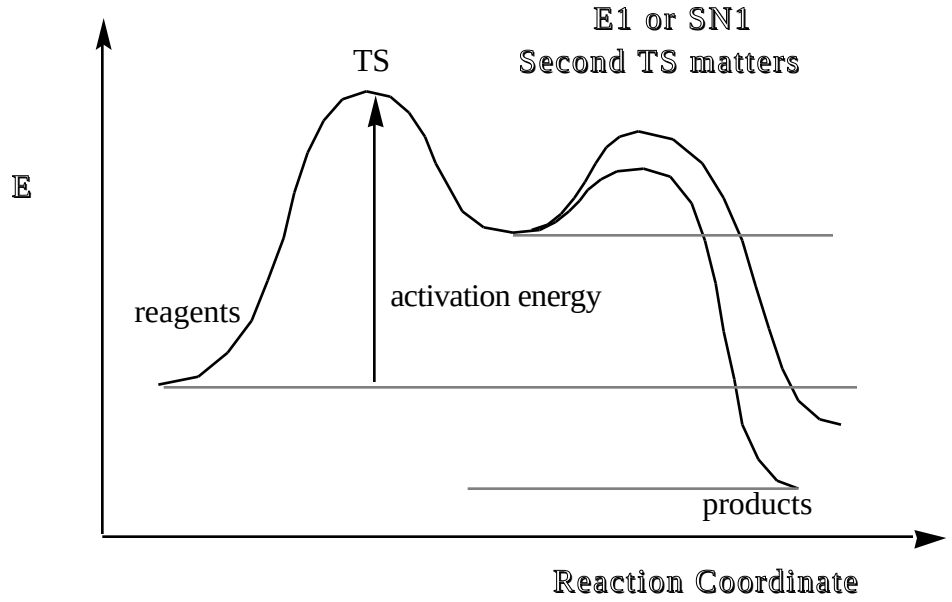


Reaction Rate

Same as with the S_N1. The slow step is the formation of the carbenium ion in both cases and the rate for that process is of course **one and the same** rate.

Competition with S_N1 Reaction

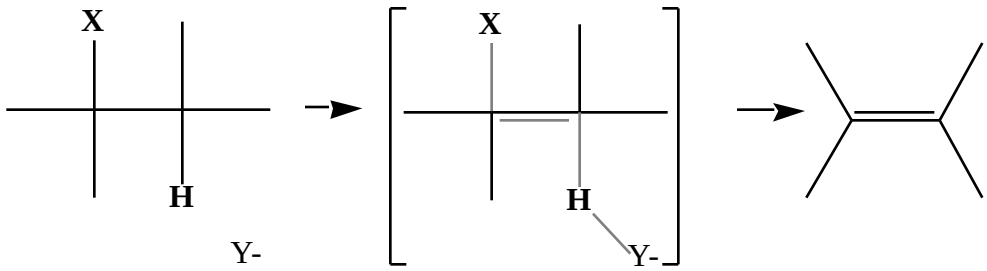
Discuss three scenarios (substitution only, elimination only, both occur).



The E2 Reaction

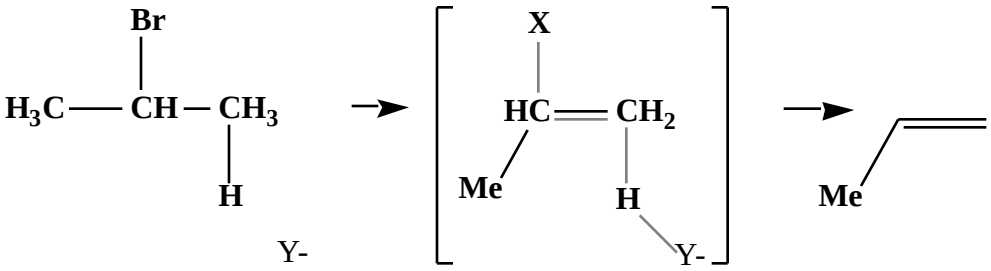
The E2 reaction is usually done with strong bases (alkoxides) and at high temperatures in an alcohol solvent (e.g. ethanol).

General Mechanism



Specific Example

Use EtO^-/EtOH at high T.



Energy Profile

Just like for the S_N2. The difference is the structure of the TS of the "one-hill" potential energy profile. (Draw it.)

Rate Equation

Bimolecular reaction. Just like for the S_N2.

Competition with S_N2 Reaction

The Nuc either acts like a base (E) or like a nucleophile (S). Which one happens one needs to find out *via* an experiment.

Stereochemistry

There are **regiochemistry** and **stereochemistry** issues! The regiochemistry goes with the rule of Saytzeff as discussed. As to the streochemistry: We can form **geometrical isomers**.

Nomenclature of Geometrical Isomers of Alkenes

For each methylene group, determine the priorities of the substituents. If the high-priority substituents are on the same side, then the molecule is *Z* (zusammen) and if they are on opposite sides, then the molecule is *E* (entgegen).

The rules:

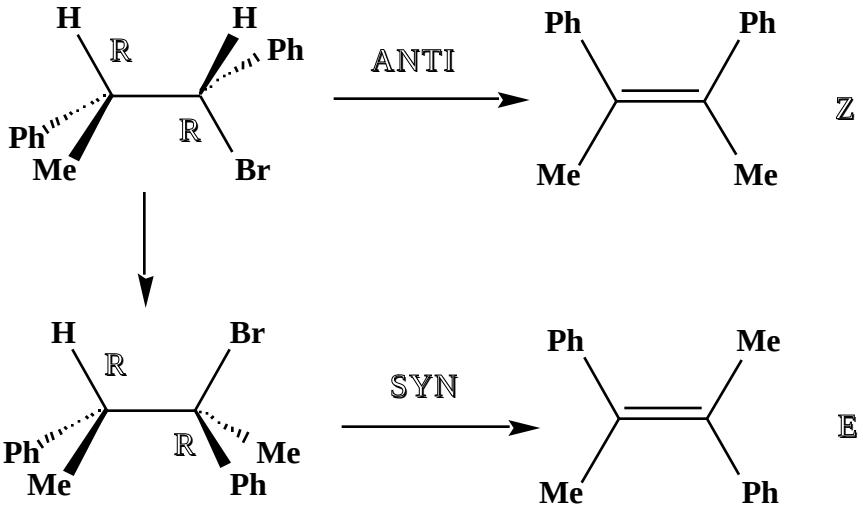
(a) always a must: H and X in the **same plane**

(b) **antiperiplanar** if possible and

(c) **syn** otherwise.

Depending as to whether (b) or (c) happens we get geometrical isomers in case we started with a halide with chiral carbons.

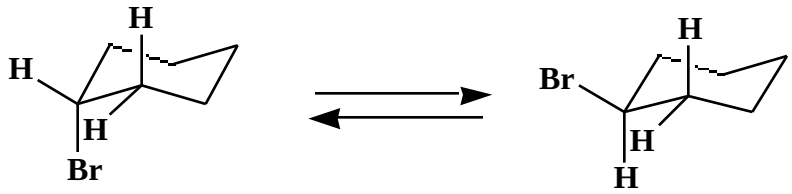
Example 1: Stereospecfic HBr Elimination



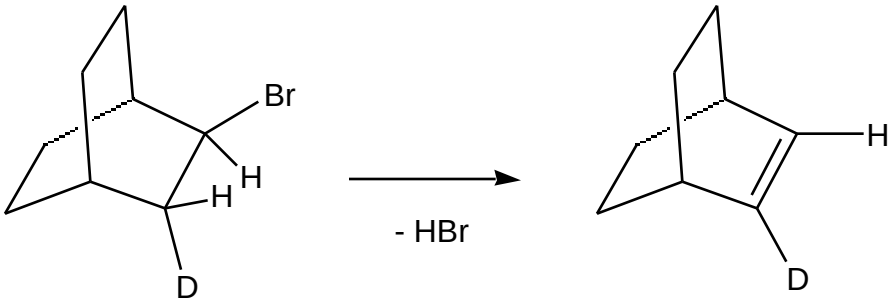
Example 2 (**at home**): Suppose we replace the methyl group "on the left C" with a second H. What are the possible products of the *anti* elimination? What are the possible products of the *syn* elimination? (Either one of the two Hs could be eliminated). Do the products have the same stability? Why not? Which one is preferred?

Example 3: Cyclohexanes

In cyclohexane, the 1,2-substituents are either *trans* or *gauche* but never *cis*. The elimination prefers the "anti" mode and thus the (a,a) isomer is the way to go. Note that the (a,a) isomer is less stable than the (e,e) isomer. Nevertheless, the interconversion requires much less energy than the elimination reaction. There will always be some (a,a) and it reacts fast, then more (a,a) is made by equilibration.



Example 4: *Syn*-Elimination

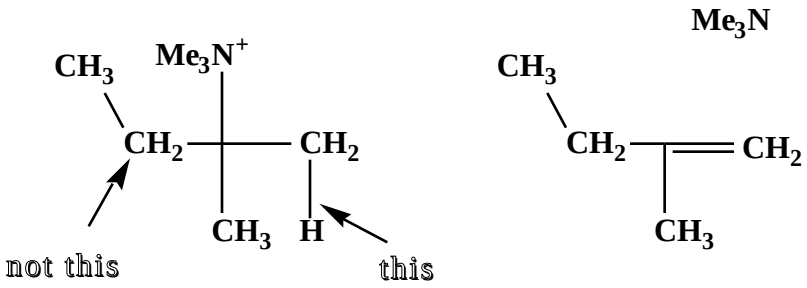


The E1cB Reaction - Hoffmann Products

Relatively rare and we will not dicuss it in as much detail as the others. Briefly, in these reactions **the proton is removed first**. If the starting material was neutral, then this removal creates a negatively charged (anionic) intermediate which then loses the leaving group.

The Classical Hoffmann Elimination

The important point is that E1cB (cum base) reactions do not lead to the **Saytzeff** product but to the **Hoffmann** product (the less substituted olefine). The classical case for the Hoffmann elimination involves **quaternary ammonium salts**.

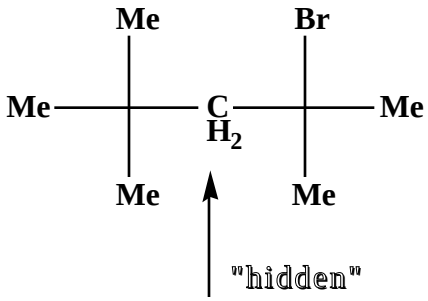


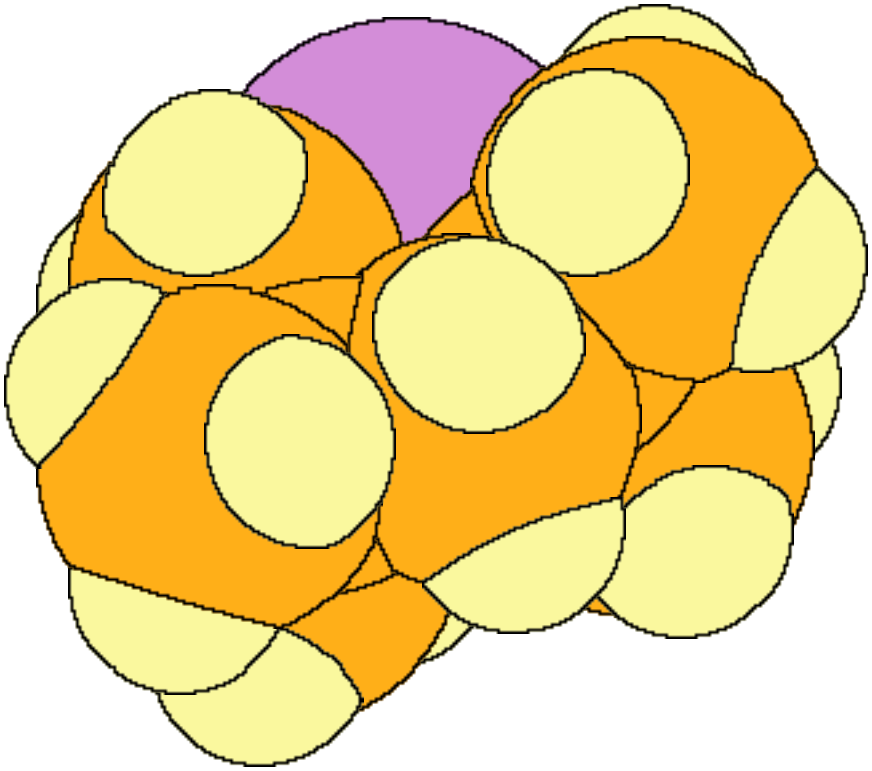
Other reasons for the production of Hoffmann Products

Steric hindrance in the removal of the β-H from the site that leads to the thermodynamically more stable product because

(a) The base is large. Example: *tert.* butoxide

(b) The β-H is "hidden" and is not approached easily by base.





Kinetic Isotope Effects

Basically the big difference between the three elimination mechanisms relates to whether the H participates in the rate limiting step (slow) step of the reaction or not. How do we know whether it does? The answer has to do with the differences between H and its heavier isotope D.

The key observation: **CD bonds have slightly higher bond dissociation energies more stable than are the CH bonds**. At this time we need not worry about why that is so. In any case, the consequence is that the activation energies for the breaking of C-H and C-D bonds are different; in other words, the C-H bonds break with higher rates than do the C-D bonds. We call the ratio **k_H/k_D the kinetic isotope effect**.

The KIE is about 7 for reactions in which the C-H/D bond is broken completely in the slow step. KIE is of course 1, if the C-H/D bond is broken in a fast step that is not the rate-limiting step of the reaction. Anything in between these values also may occur and the magnitude tells us the degree by which the C-H/D bond is broken in the slow step of the reaction.

Mechanism	Kinetic Isotope Effect
E1	1
E2	1< KIE < 6
E1cB	close to 7

Substitution and Elimination

The Nature of the Alkyl Halide

(a) Methyl and primary halides do S_N2 and E2 (with strong base). No unimolecular chemistry.

(b) Tertiary halides undergo solvolysis reactions via S_N1 and E1 and they can do E2 eliminations with stronger bases.

(c) Allylic and benzylic halides do S_N1 pretty clean.

(d) Secondary halides can do any of the mechanisms. The outcome can be manipulated significantly through choice of reaction conditions.

Nucleophilicity of the Base

Primary alkyl halides do S_N chemistry with any base.

Tertiary alkyl halides greatly favor elimination unless the base is very weak (water, alcohol) as in solvolysis conditions.

Secondary alkyl halides:

Strong nucleophile:	S_N2
Weak nucleophile:	S_N1
Strong Base:	E2

The Solvent

Solvents are classified regarding (a) their polarity, (b) their H bonding capability and (c) their proton donating/accepting capability. What matters most for these reactions here is the polarity.

Bimolecular reactions have less charged transition states, unimolecular reactions have highly charged transition states. Polar solvents stabilize the charged transition states, that is polar solvents increase the rates of S_N1 and E1. S_N2 and E2 reactions are affected much less by solvent polarity.

Solvents with protic H can solvate anions and reduce the nucleophilicity of the nucleophile.

Nucleophile Concentration

High concentration makes the bimolecular process faster while the concentration does not affect the unimolecular process.

Temperature

More elimination the higher the temperature. Entropy term kicks in more ($T\Delta S$).

Syntheses with S_N and E Chemistry

NUC	Carbon Type	Product
alkoxide	1 and 2	ether
alkoxide	3	olefine
hydroxide	1 and 2	alcohol
cyanide	1 and 2	nitrile
sulfide	1 and 2	thioether
carboxylate	1 and 2	ester
iodide	1 and 2	iodo compounds
amines	1 and 2	ammonium ions