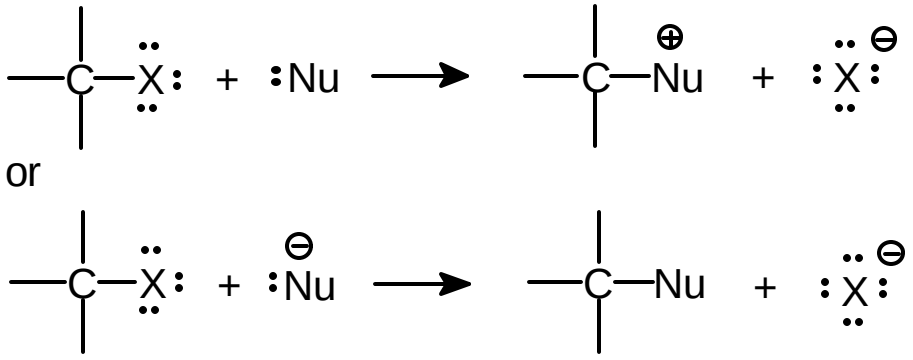
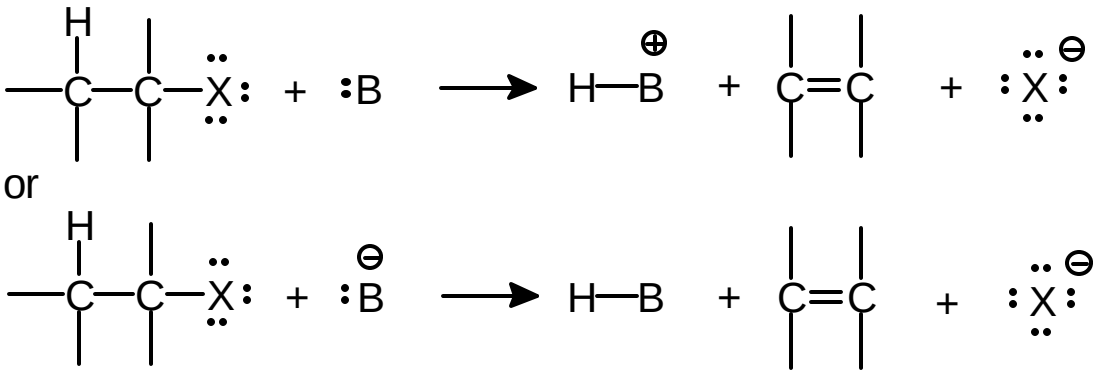
Reactions of Alkyl Halides in Which the Bond Between Carbon and Halogen is Broken — An Overview

Alkyl halides are prone to undergoing nucleophilic substitutions and base promoted eliminations. In either reaction type the alkyl halide reactant is called the *substrate*. And in either reaction type the chemical that reacts with the substrate is a Lewis base. Furthermore, the substrate loses the halogen in both of these reaction types – it is not present in the organic product; thus, the halogen is referred to as a *leaving group*.

In nucleophilic substitutions the Lewis base acts as a nucleophile and will be attached to a carbon in the product, often (but not always) the same carbon that held the leaving group (halogen) in the substrate –



In base promoted eliminations the Lewis base (which is usually neutral or negatively charged) functions as a Bronsted-Lowry base and takes a proton from the substrate. Usually this proton is a β-proton, a proton that is attached to a carbon that is attached to the carbon that holds the leaving group. The product that results from the departure of both the β-hydrogen and halogen from the substrate will have a double bond –



Aliphatic nucleophilic substitutions, as shown above, usually take place via mechanisms we call S_N1 and S_N2 – Substitution nucleophilic unimolecular and Substitution nucleophilic bimolecular.

Base promoted eliminations, as shown above, usually take place via mechanisms we call E1 and E2 – Elimination unimolecular and Elimination bimolecular.

Since all four of these reaction mechanisms, two of which lead to substitution products and two of which lead to elimination products, require essentially the same materials (the halogen containing substrate and a Lewis base) it will be the case that they will often be in competition with each other. Sometimes one will dominate. Which one this is will depend on the nature of the substrate, the nature of the Lewis base, the solvent employed, and other factors.

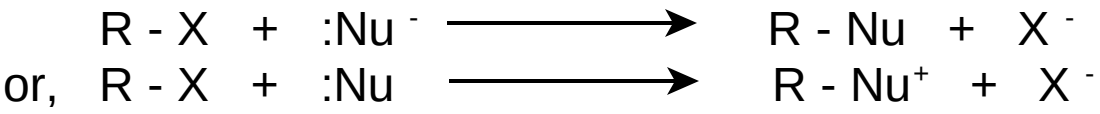
Alkyl Halides in Nucleophilic Substitutions —

Halide ions, except F^-, are weak bases since the conjugate acids, HX (except HF), are strong acids.

Acid	pK_a		Conjugate Base	
HI	-9	strongest acid	I^-	weakest base
HBr	-8.5		Br^-	
HCl	-6.5		Cl^-	
H_3O^+	-1.74		H_2O	
HF	3.18		F^-	
RCOOH	4.5		$RCOO^-$	
H_2S	7.0		HS^-	
HCN	9.21		CN^-	
NH_4^+	9.25		NH_3	
H_2O	15.7		OH^-	
ROH	17 to 20	weakest acid	RO^-	strongest base

Concomitantly, halogen attached to sp^3 carbon can be easily (except F) displaced by stronger bases (nucleophiles).

Thus, a typical reaction of alkyl halides is nucleophilic substitution:



R - X = substrate, X = leaving group, :Nu = nucleophile

Halide ions are good leaving groups (except F^-).

(Aryl and vinyl halides undergo this reaction with extreme difficulty.)

Because of the many nucleophiles available, this reaction is very useful in synthesis. The table below lists just a few possibilities.

Nucleophile	Substrate	Product
R-C≡C: $^-$	CH_3Br	R-C≡C-CH_3
:N≡C: $^-$	CH_3Br	:N≡C-CH_3
	CH_3Br	HO-CH_3
	CH_3Br	I-CH_3
H_3N:	CH_3Br	$H_3N^+-CH_3$ Br^-

Halide exchange –

Preparation of alkyl fluorides and iodides:

$$R\text{-}Cl \xrightarrow{SbF_3} R\text{-}F$$

eg $$CCl_4 \xrightarrow{SbF_3} CF_2Cl_2$$

(dichlorodifluoromethane: Freon-12)

$$R\text{-}X + NaI \xrightarrow{\text{acetone}} R\text{-}I + NaX\ (ppt.)$$

X = Cl, Br

Preparation of alcohols –

$$R\text{-}X + KOH \longrightarrow ROH + KX$$

X = Br, Cl

Best if R is methyl, primary; may not work if R is tertiary (owing to competition from the elimination reaction that would convert the alkyl halide to an alkene).

Kinetics of Nucleophilic Aliphatic Substitution

Consider: $CH_3I + OH^- \longrightarrow CH_3OH + I^-$

If reaction occurs by collision between CH_3I and OH^-:

rate = $k_2[CH_3I][OH^-]$, where k_2 is a constant.

⇑ This is observed. We say the rate equation is first order in substrate (CH_3I) and first order in nucleophile (OH^-) – second order, overall. By this we mean that the concentration of substrate is raised to the first power as is the concentration of nucleophile. The overall order is the sum of the concentration exponents.

Consider: $(CH_3)_3C\text{-}I + OH^- \longrightarrow (CH_3)_3OH + I^-$

rate = $k_1[(CH_3)_3C\text{-}I]$, where k_1 is a constant.

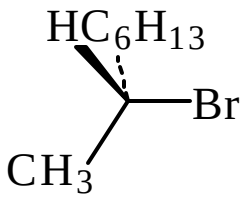
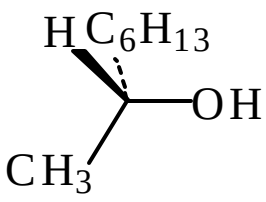
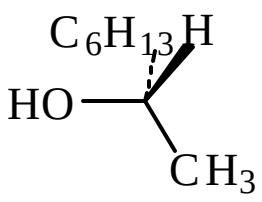
⇑ This is observed. In this case the rate equation is first order in substrate and zeroth order in nucleophile – first order, overall.

To account for differences in kinetics, and other observations: two mechanisms for aliphatic nucleophilic substitution — S_N2 and S_N1.

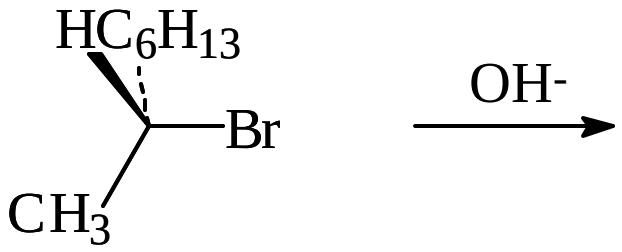
In the S_N2 (Substitution, Nucleophilic, Bimolecular) mechanism the reaction takes place in one step when the substrate and nucleophile collide. Since both substrate and nucleophile are involved in this step, the rate is second order; it depends on [substrate] and [nucleophile].

In the S_N1 (Substitution, Nucleophilic, Unimolecular) mechanism the reaction takes place in two steps. In the first — slow — step a carbocation is formed by ionization of the halide. The second — fast — step is the reaction of this carbocation with the nucleophile. The rate of this reaction depends on the rate of the first step: the formation of the carbocation. Therefore, the rate is first order; it depends on [substrate] and not on [nucleophile] since the nucleophile is not involved in the first step.

Experiment:

		
(-)-2-bromooctane	(-)-2-octanol	(+)-2-octanol
$[\alpha]= -36^o$	$[\alpha]= -10.3^o$	$[\alpha]= +10.3^o$

Under conditions where second-order kinetics is followed:



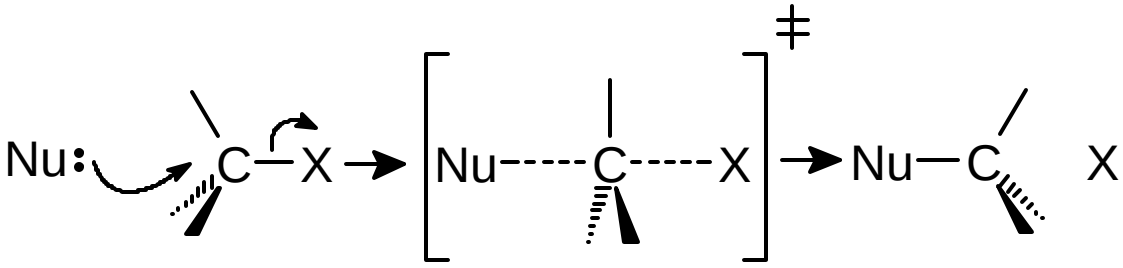
(-)-2-bromooctane

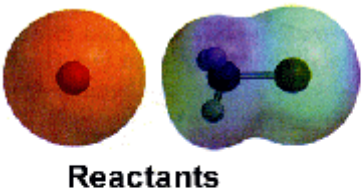
$[\alpha]= -36^o$

(+)-2-octanol
$[\alpha] = +10.3^o$,
measured at the
end of the reaction.

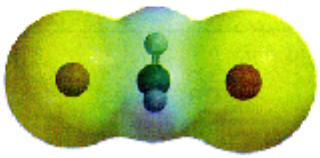
So, the -OH group is <u>not</u> located where the Br was, but rather is on the other side of the carbon atom: the configuration is *inverted*.

An S_N2 reaction proceeds with inversion of configuration (Walden inversion). Every molecule is inverted owing to backside attack of the nucleophile; *ie*, the nucleophile attacks the carbon holding the leaving group on the side opposite the leaving group. As this happens the leaving group departs and the nucleophile becomes attached to the carbon that had held the leaving group.

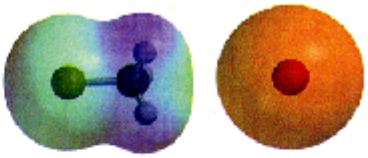




Reactants



Transition State



Products

Red = negative charge
Blue = positive charge
Note that charge at substrate carbon does not change much on going from reactants to transition state.

<u>Reactivity in S_N2 Mechanism — Effect of Substrate Structure</u> —

Electronic effects (electron donation or withdrawal) of groups attached to the site of nucleophilic attack in the substrate are relatively unimportant since there is not a large net electron density change at this site in going from reactants to transition state.

Steric factors (*ie* bulk of groups attached to or near the site of nucleophilic attack) are important since bulky groups block attack by the nucleophile and decrease the probability of a "successful" collision.

Therefore, in S_N2 reactions, order of reactivity =

$CH_3X > 1^o > 2^o > 3^o$

S_N1 Reaction Mechanism —

$(CH_3)_3C\text{-}I + OH^- \longrightarrow (CH_3)_3OH + I^-$

rate = $k_1[(CH_3)_3C\text{-}I]$

Since the rate does not involve [OH^-], the reaction whose rate is being measured does not involve OH^-.

Consistent with ☞

1) $(CH_3)_3C\text{-}I \xrightarrow{\text{slow}} (CH_3)_3C^+ + I^-$

2) $(CH_3)_3C^+ + OH^- \xrightarrow{\text{fast}} (CH_3)_3C\text{-}OH$

1) is the rate determining step.

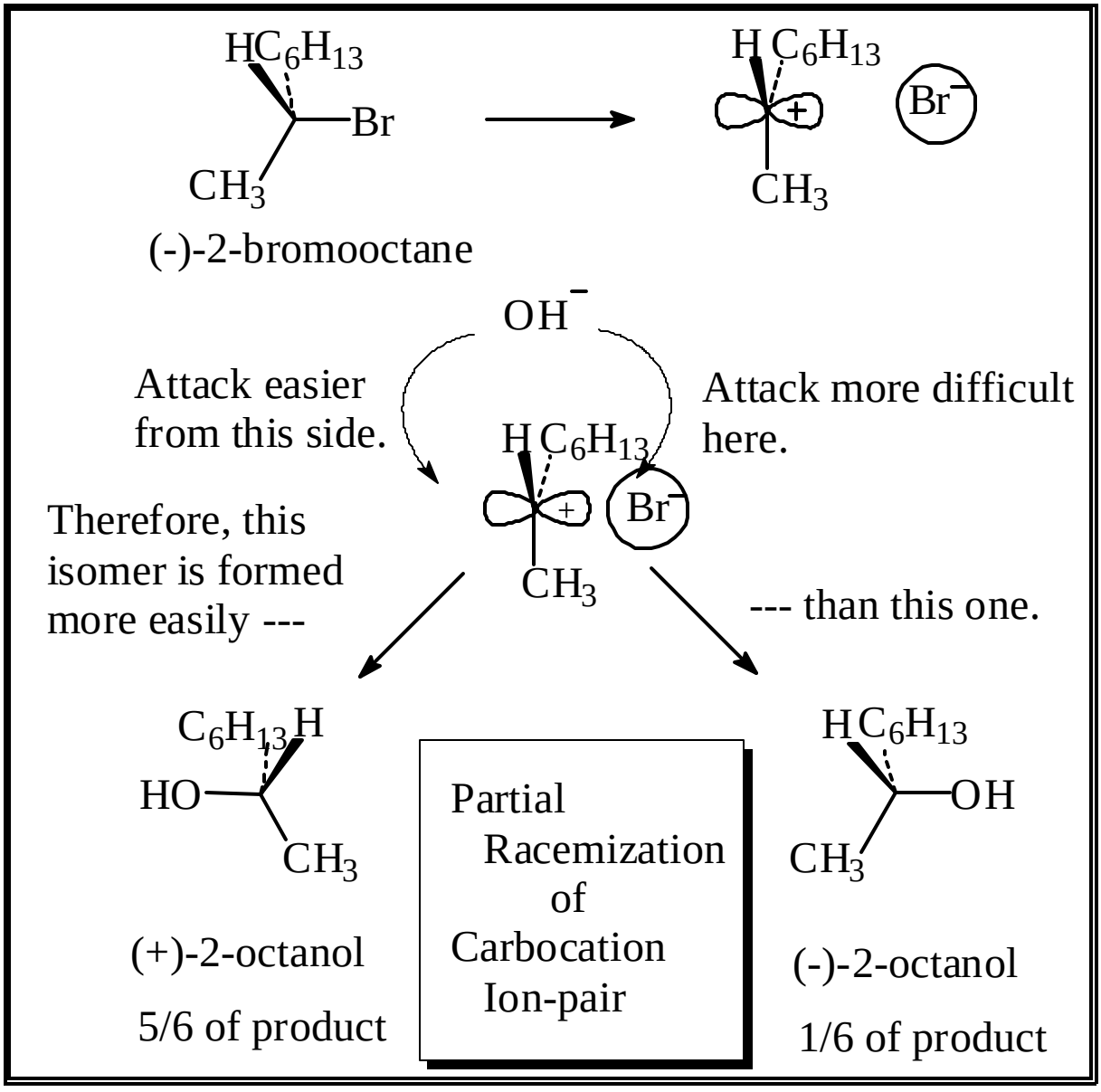
Stereochemistry of the S_N1 Mechanism —

Under conditions where first order kinetics is observed:

(-)-2-bromooctane $\xrightarrow{OH^-,\ H_2O}$

2/3 (+)-2-octanol + 1/3 (±)-2-octanol
⇑ from inversion ⇑ from racemization

This is consistent with a planar (sp^2) carbocation intermediate —



If the carbocation were completely free of the halide ion, racemization would be complete. This case is more typical.

Reactivity in S_N1 Mechanism — Effect of Substrate Structure —

In the S_N1 mechanism a carbocation is formed in the rate limiting step. The more stable the carbocation the smaller its $\Delta G^{\ddagger}$. Electron releasing groups (like alkyl groups) stabilize the carbocation. So, the order of reactivity for substrates is $3^o > 2^o > 1^o >$ methyl.

Effect of the Nucleophile on Reactivity in Aliphatic Nucleophilic Substitutions —

S_N2 —
Since the nucleophile is involved in the rate limiting step the more aggressive it is in terms of its Lewis basicity toward the substrate (its *nucleophilicity*) the faster the reaction will be.
> Nucleophilicity roughly parallels basicity when comparing nucleophiles that have the same attacking atom. CH_3O^- is both more basic and more nucleophilic than HO^-.
> Nucleophilicity usually increases going down a column of the periodic table. HS^- is more nucleophilic than HO^-, although it is less basic.
> Negatively charged nucleophiles are more reactive than neutral ones when the attacking atom is the same. NH_2^- is more nucleophilic than NH_3.

S_N1 —
Since the nucleophile is not involved in the rate limiting step its nucleophilicity does not affect the rate of reaction. However, since the S_N1 and S_N2 reactions are in competition changing the nucleophile from a weak one to a strong one may cause the reaction mechanism to change from S_N1 to S_N2.

Effect of the Leaving Group on Reactivity in Aliphatic Nucleophilic Substitutions —

The leaving group leaves in the rate limiting step in both S_N1 and S_N2 reactions. The better the leaving group the faster these reactions will be. Generally, the less basic the departed leaving group the better it is as a leaving group.

Effect of the Solvent on Reactivity in Aliphatic Nucleophilic Substitutions —

S_N2 —
Protic solvents (those with a proton attached to oxygen or nitrogen) tend to reduce the nucleophilicity of a nucleophile by hydrogen bonding or ion-dipole interactions (*solvation*). By crowding around the nucleophile these solvent molecules impede it.

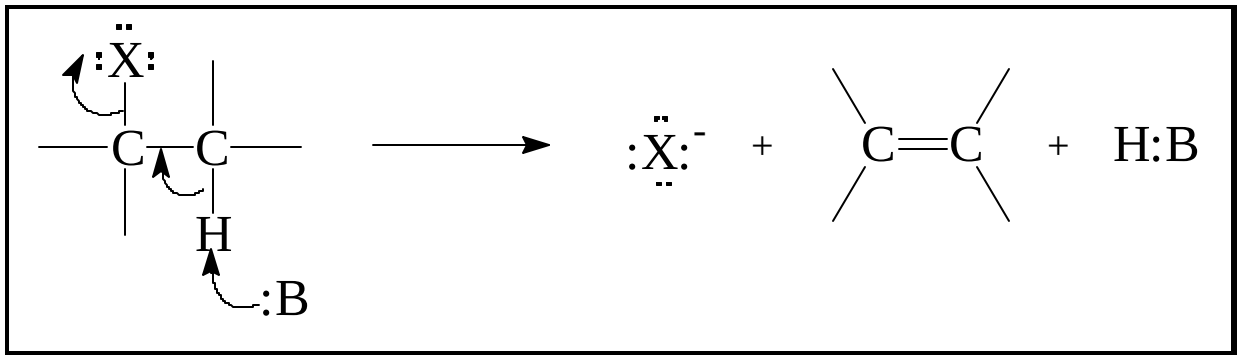
On the other hand, the partially negative ends of aprotic polar solvents like acetonitrile and N,N-dimethylformamide solvate cations. Since anions and cations tend to travel somewhat paired up, these solvents free the anion to be more nucleophilic since it is no longer encumbered by a cation.

S_N1 —

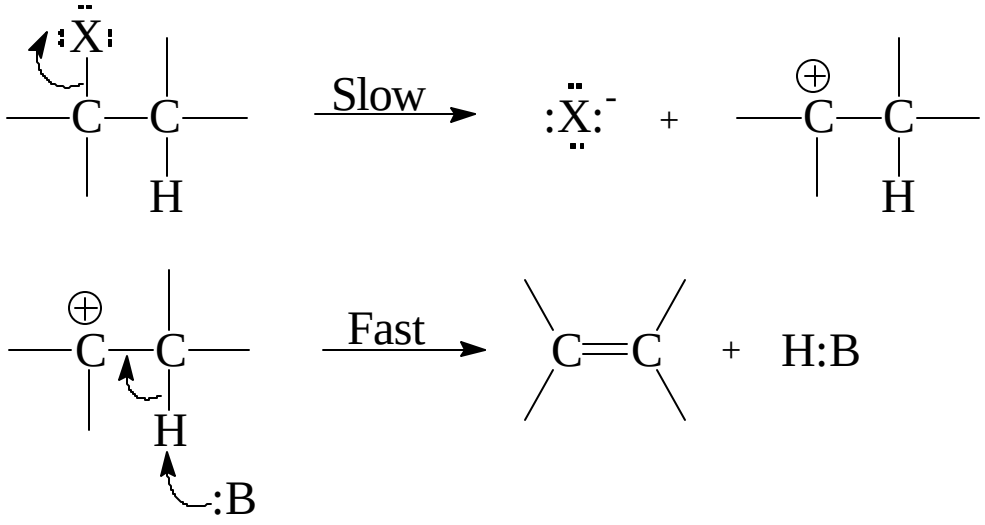
In this mechanism, the slow step involves the heterolytic breaking of the carbon - leaving group bond. If the leaving group is an anion the transition state is much more polar than the reactant. Polar solvents can stabilize the incipient carbocation and leaving group anion through solvation. Thus, polar solvents usually speed up these reactions.

Elimination Reactions: E2 and E1 –

E2: Elimination, bimolecular (second order kinetics).



E1: Elimination, unimolecular (first order kinetics) —



Important only for 3° substrates at low base concentration.

Reactivity toward E1 & E2: $3^o > 2^o > 1^o$

- ☞ E2 — order of stability of alkenes formed.
- ☞ E1 — order of stability of the carbocations being formed.

Evidence in support of the E1 mechanism —

A) Kinetics — first order in substrate, zeroth order in base: first order overall.

B) Rearrangements observed, suggesting carbocation intermediate.

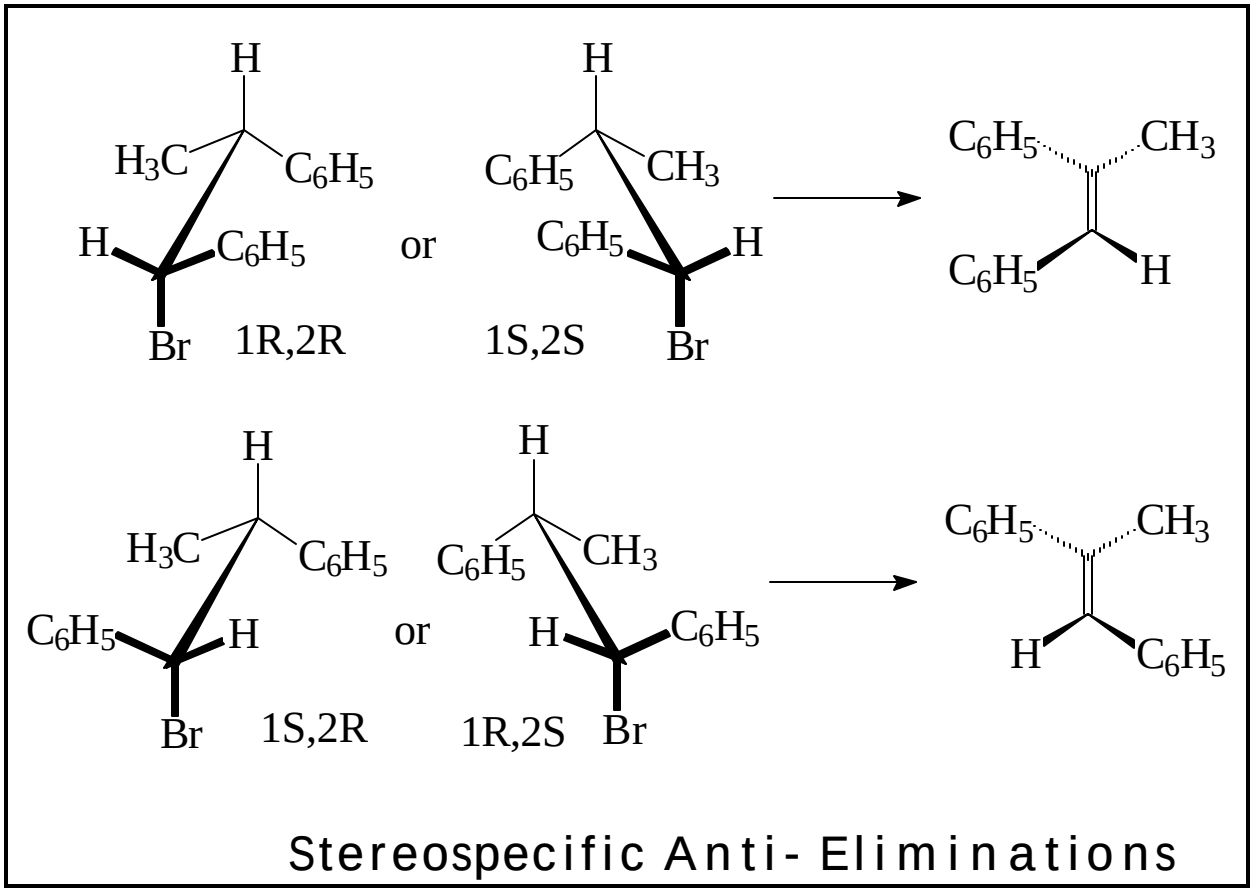
Evidence in support of the E2 mechanism —

A) Kinetics — first order in substrate, first order in base: second order overall.

B) No rearrangements, suggesting no carbocation intermediates.

C) Anti- elimination of H and X.

This requirement of an anti orientation of H and X (Br) suggests a one step mechanism, because if an intermediate were involved (*eg* a carbocation) free rotation would destroy the *stereospecificity.*



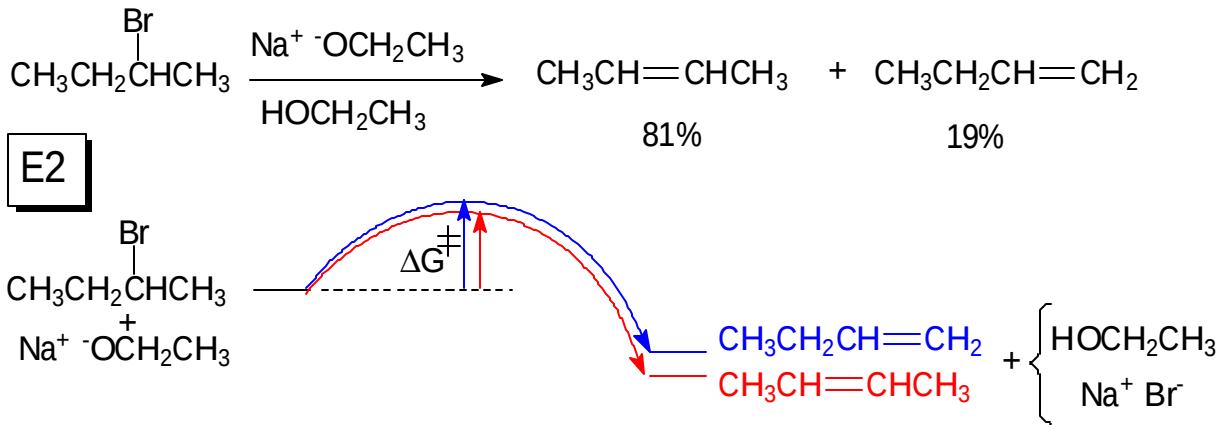
Stereospecific Anti- Eliminations

Regioselectivity in Eliminations —

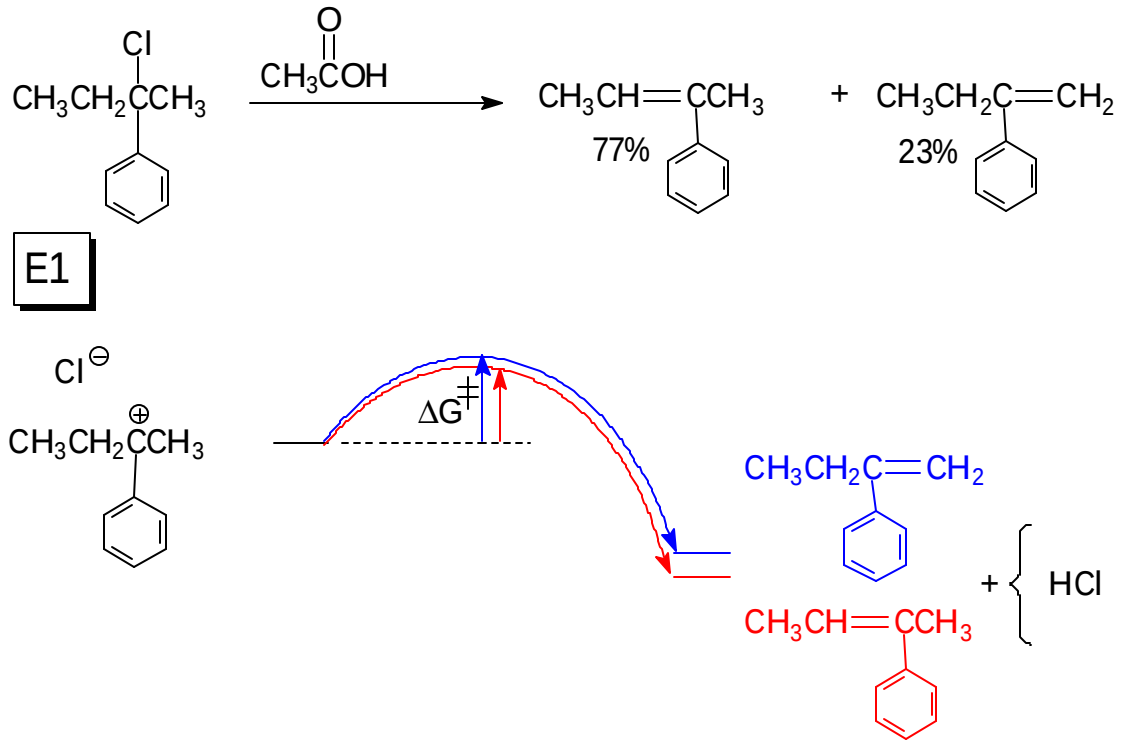
Zaitsev's (Saytzeff's) Rule –
In the elimination of HX from an alkyl halide, the more highly substitutied alkene product is preferentially formed (assuming that more than one structural isomer can form). [This preference is not usually strong; often a mixture of products is formed.]

We know that more highly substituted alkenes are more stable, so this rule is telling us that the more stable alkene will form preferentially. This makes sense for both E2 and E1 eliminations –

E2: This reaction occurs in one step. $\Delta G^{\ddagger}$ should be smaller for the formation of the more stable product.



E1: Once the carbocation (or rearranged carbocation) forms, the question is which β-hydrogen will be removed? Again, $\Delta G^{\ddagger}$ should be smaller for the formation of the more stable product.



Summary —

Halide Type	S_N1	S_N2	E1	E2
RCH_2X (primary)	Does not occur: 1^o carbocation too unstable	Favored/ for steric reasons/ by high conc. of good nucleophile/ at room temp	Does not occur: 1^o carbocation too unstable	Occurs with strong base at high temp.
R_2CHX (secondary)	Depends on conditions: favored by low conc of weak nucleophile/ allyl & benzyl groups	Competes with E2. Favored by high conc of good nucleophile/ weak base	Depends on conditions: favored by low conc of weak base/ allyl & benzyl groups	Favored by high conc of strong base at high temp.
R_3CX (tertiary)	Favored in hydroxylic solvents	Does not occur	Competes with S_N1/ favored by poor nucleophile	Favored when bases are used: subst. alkene is produced.