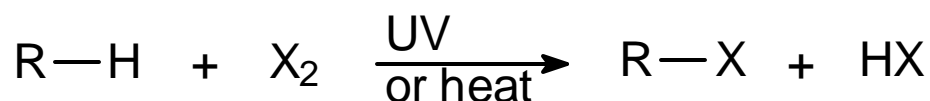


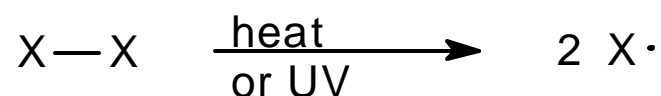
Preparation of Alkyl Halides, R-X

Reaction of alkanes with Cl_2 & Br_2
(F_2 is too reactive, I_2 is unreactive):

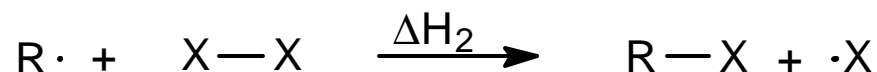


This mechanism involves a *free radical chain reaction*. A chain reaction involves a series of steps *in which a product formed in a later step is a reactant in an earlier step*.

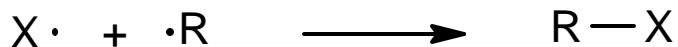
Initiation-



Propagation-



Termination-



ΔH° in kJ/mole

R =	CH ₃	1° R	2° R	3° R
$\Delta H_1, \text{Cl}_2$	+6	-12	-31	-42
$\Delta H_1, \text{Br}_2$	+72	+54	+35	+24
$\Delta H_2, \text{Cl}_2$	-108	-95	-96	-87
$\Delta H_2, \text{Br}_2$	-100	-92	-87	-70

Note that the second propagation step (ΔH_2) is quite exothermic in all cases. The first step (ΔH_1) is less exothermic or endothermic. It is reasonable to conclude that the first step would have the larger ΔG^\ddagger and is rate limiting. It also follows that the rate of reaction for substitution of hydrogens by halogens would be $3^\circ > 2^\circ > 1^\circ > \text{methane}$. This is also the order of stability of the alkyl free radicals that are formed: the more stable intermediate radical is formed faster.

At room temperature, the relative rate of replacement of hydrogen atoms in alkanes by chlorine is $3^\circ : 2^\circ : 1^\circ = 5.0 : 3.5 : 1.0$ (per hydrogen).

At 125° C, the relative rate of replacement of hydrogen atoms in alkanes by bromine is

$3^\circ : 2^\circ : 1^\circ = 1600 : 80 : 1$ (per hydrogen).

Bromination is more selective than chlorination.

Owing to its lack of selectivity, free radical chlorination is of limited usefulness in synthesis.

Another problem with free radical chlorination in synthesis is polychlorination.

Bromination is more selective than chlorination but polybromination can be a problem.

Alkyl Halides from Alcohols



X = Cl, Br, I

Reactivity of ROH: $3^\circ > 2^\circ > 1^\circ$

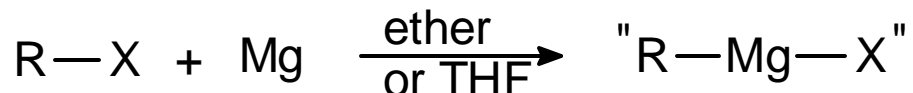
Rearrangement of 2° R (to 3°) possible; rearrangement of 1° (to 2° or 3°) occasionally occurs.

Reactivity of HX: $\text{HI} > \text{HBr} > \text{HCl}$

Other reagents that are used with 1° & 2° alcohols:
thionyl chloride, SOCl_2 , to make alkyl chlorides;
phosphorous tribromide, PBr_3 , to make alkyl bromides;
phosphorous + iodine, $\text{P} + \text{I}_2$, to make alkyl iodides.
Rearrangements are less likely with these reagents.

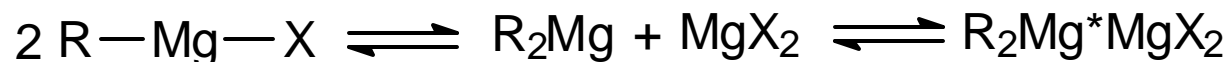
Reactions of Alkyl Halides

Formation of Grignard Reagents —



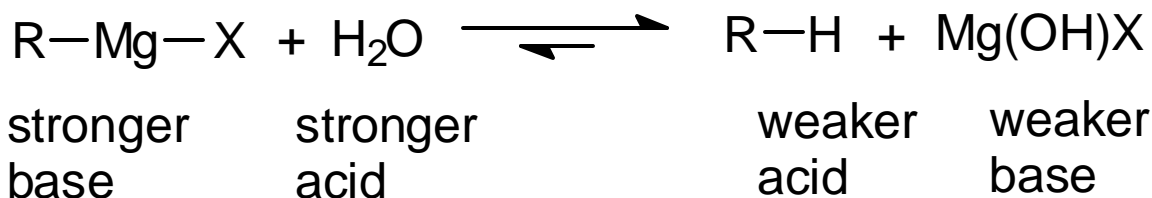
R = 1°, 2°, or 3° alkyl, vinylic, aromatic;
vinylic and aromatic are less reactive.

X = Cl, Br, I; usually not F; reactivity: I > Br > Cl.
Structure in solution – complex mixture – partly:



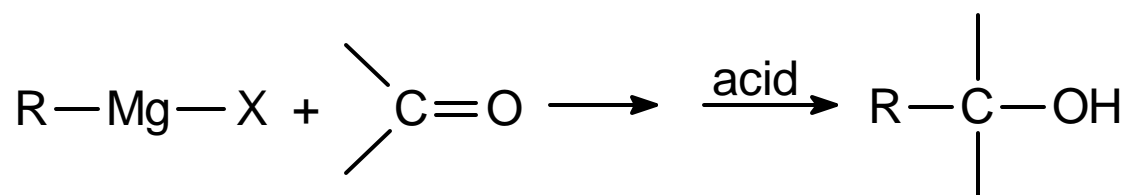
but acts like $\overset{\delta-}{\text{R}}-\overset{\delta+}{\text{Mg}}-\overset{\delta-}{\text{X}}$; thus the R-group has both nucleophilic and basic character.

Base – If the R-group is alkyl, R-Mg-X will react with any material that is more acidic than an alkane, eg



Thus, R-Mg-X cannot be prepared in the presence of any material that is slightly acidic, including compounds with H attached to O or N.

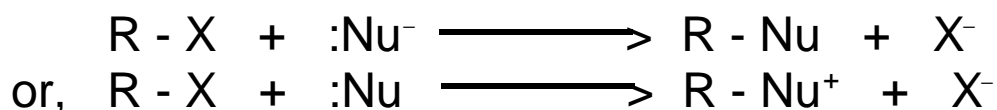
A major reason for making Grignard reagents is to synthesize alcohols by reacting the Grignard with carbonyl compounds:



Alkyl Halides in Nucleophilic Substitutions —

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

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).

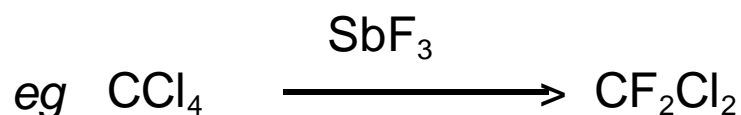
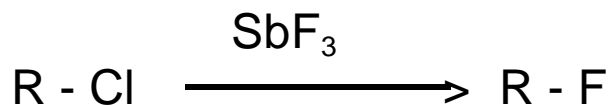
(Aryl and vinyl halides undergo this reaction with extreme difficulty.)

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

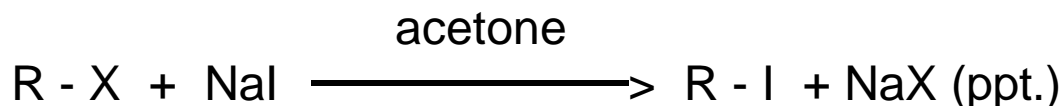
Nucleophile	Substrate	Product
$R-C\equiv C:^-$	CH_3Br	$R-C\equiv C-CH_3$
$:N\equiv C:^-$	CH_3Br	$:N\equiv C-CH_3$
$H\ddot{O}^-$	CH_3Br	$HO-CH_3$
$:\ddot{I}^-$	CH_3Br	$I-CH_3$
$H_3N:$	CH_3Br	$H_3N^+-CH_3 \quad Br^-$

Halide exchange –

Preparation of alkyl fluorides and iodides:

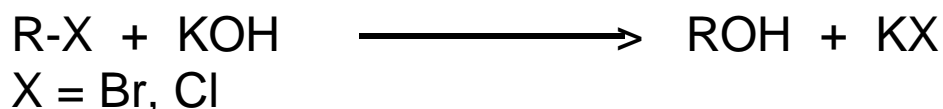


(dichlorodifluoromethane: Freon-12)



X = Cl, Br

Preparation of alcohols –



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



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

$$\text{rate} = k_2[\text{CH}_3\text{I}][\text{OH}^-], \text{ where } k_2 \text{ is a constant.}$$

[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.



$$\text{rate} = k_1[(\text{CH}_3)_3\text{C-I}], \text{ where } k_1 \text{ is a constant.}$$

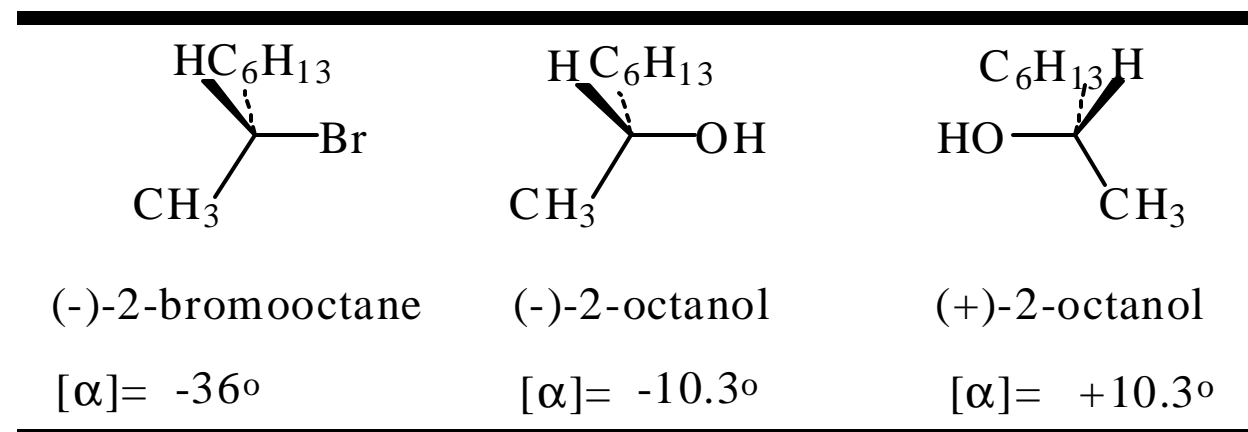
[This is observed. In this case the rate equation is first order in substrate and zeroth order in nucleophile – first order, overall.

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

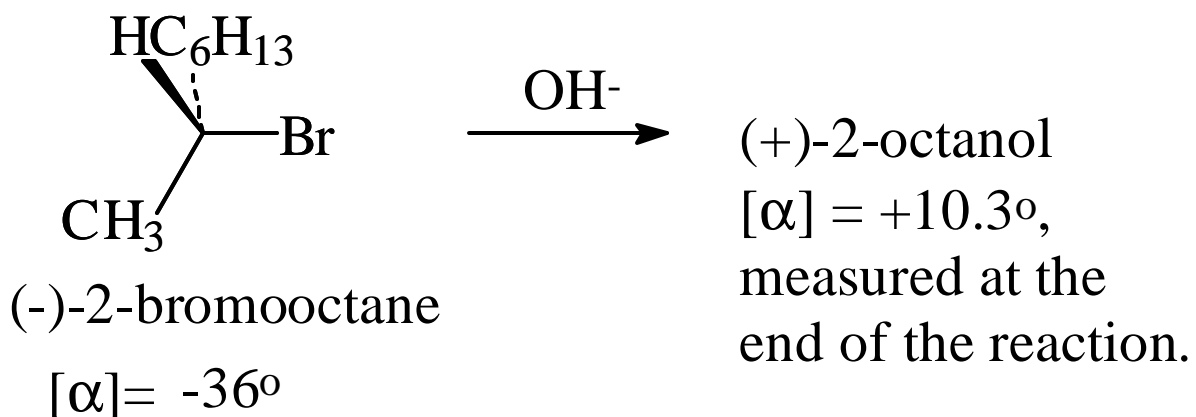
In the S_N2 (Substitution, Nucleophilic, Bimolecular) mechanism the reaction takes place in one step when the substrate and nucleophile collide. Since both substrate and nucleophile are involved in this step, the rate is second order; it depends on [substrate] and [nucleophile].

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:

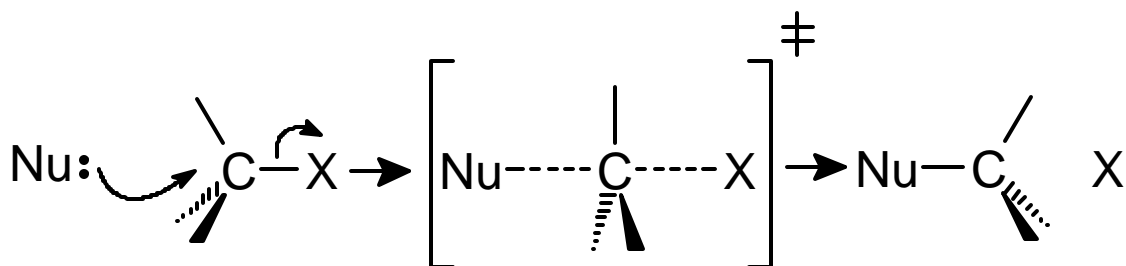


Under conditions where second-order kinetics is followed:



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

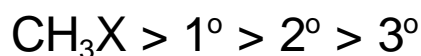
An S_N2 reaction proceeds with inversion of configuration (Walden inversion). Every molecule is inverted owing to backside attack of the nucleophile; *ie*, the nucleophile attacks the carbon holding the leaving group on the side opposite the leaving group. As this happens the leaving group departs and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

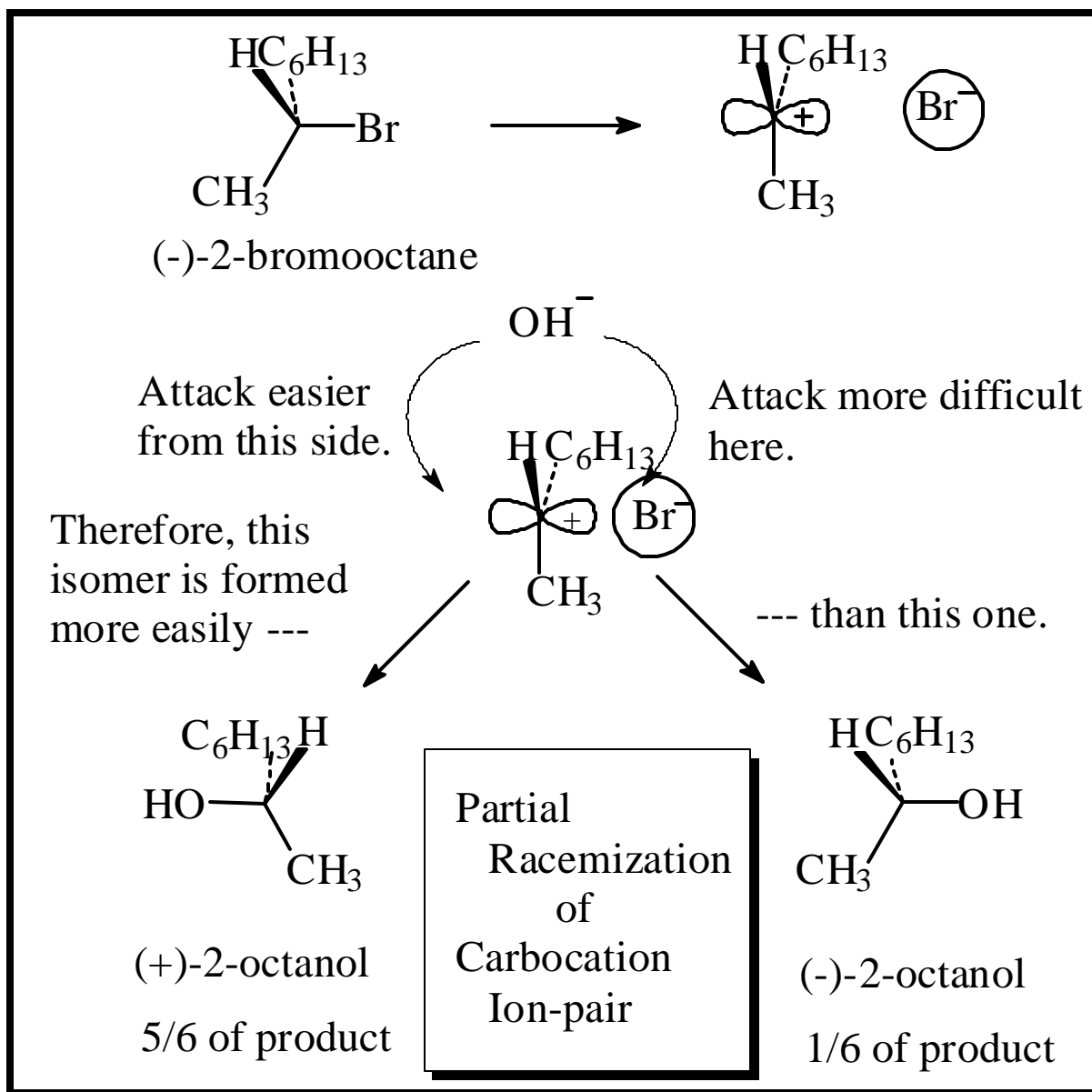


Reactivity in S_N2 mechanism — effect of substrate structure —

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 =

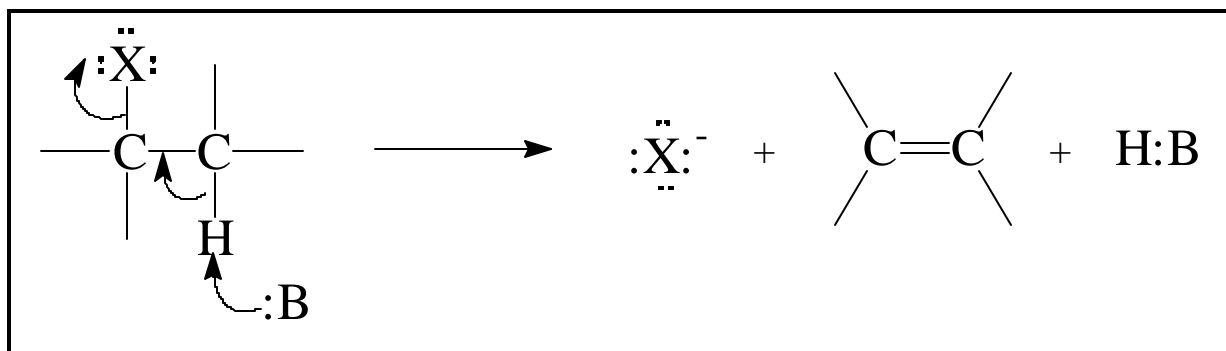




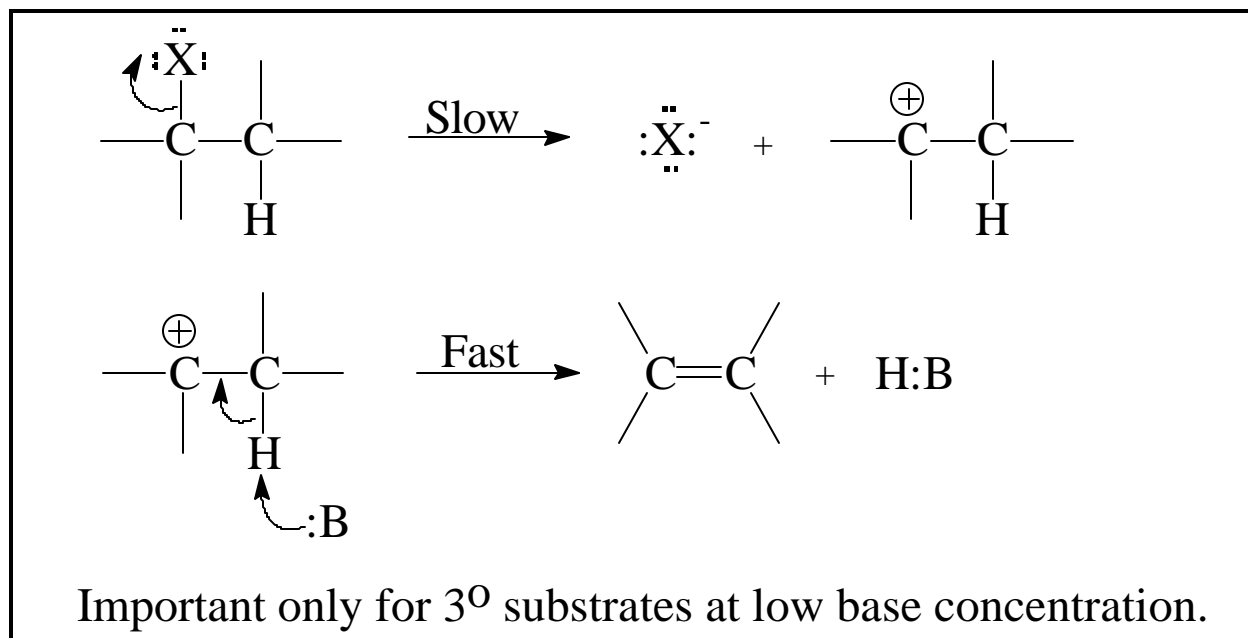
If the carbocation were completely free of the halide ion, racemization would be complete. This case is more typical.

Elimination Reactions: E2 and E1 –

E2: Elimination, bimolecular (second order kinetics).



E1: Elimination, unimolecular (first order kinetics) —



Reactivity toward E1 & E2: 3° > 2° > 1°

- L E2 — order of stability of alkenes formed.
- L 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) Same effect of structure on reactivity as in S_N1.

C) Rearrangements observed, suggesting carbocation intermediate.

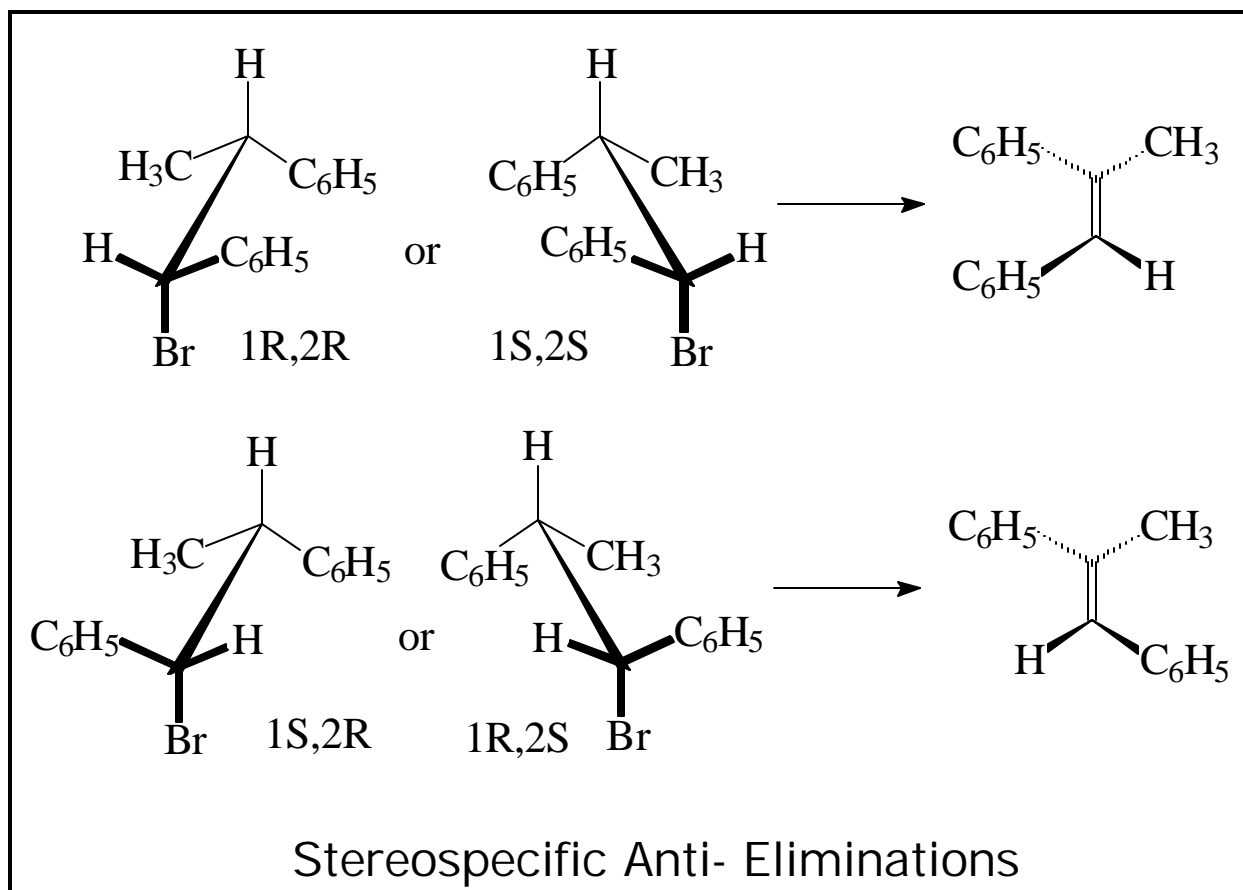
Evidence in support of the E2 mechanism —

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*.



Halide Type	S _N 1	S _N 2	E1	E2
RCH ₂ X (primary)	Does not occur: 1° carbocation too unstable	Favored/ for steric reasons/ by high conc. of good nucleophile/ at room temp	Does not occur: 1° carbocation too unstable	Occurs with strong base at high temp.
R ₂ CHX (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 ₃ CX (tertiary)	Favored in hydroxylic solvents	Does not occur	Competes with S _N 1/ favored by poor nucleophile	Favored when bases are used: subst. alkene is produced.