Nucleophilic Substitution and Elimination

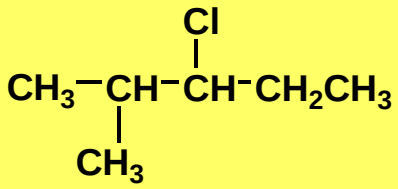
Alkyl Halides

A. Nomenclature

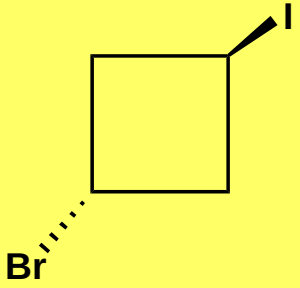
1. IUPAC - add flouro-
   chloro-
   bromo-
   iodo-

   } to alkane name

examples:

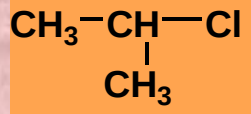


2-methyl-3-chlorohexane

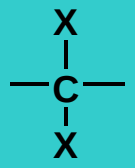
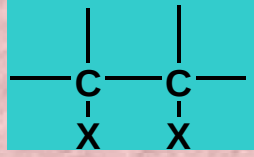


trans-1-bromo-3-iodocyclobutane

2. common names

CH_3Cl	methyl chloride
CH_3CH_2Cl	ethyl chloride
	*i*-propyl chloride
CH_2Cl_2	methylene chloride
$CHCl_3$	chloroform
CCl_4	carbon tetrachloride

3. special names

	geminal dihalide
	vicinal dihalide

B. Industrial uses

a. solvents: CH_2Cl_2, $CHCl_3$, CCl_4

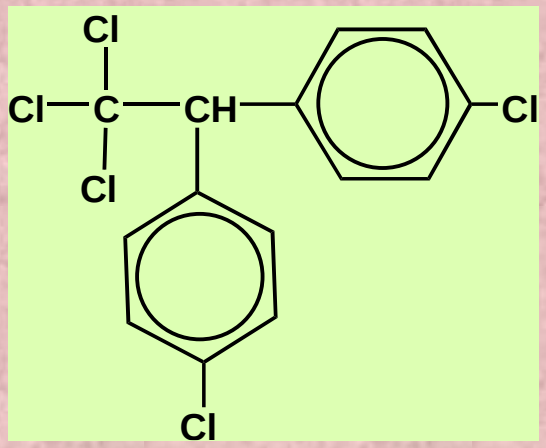
b. refridgerents:

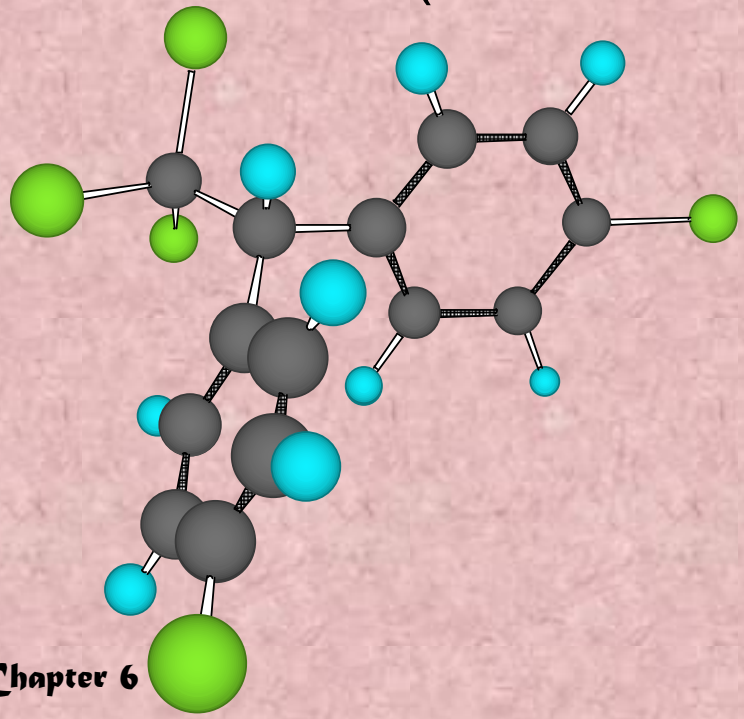
CF_2Cl_2 - Freon-12 (eats O_3)

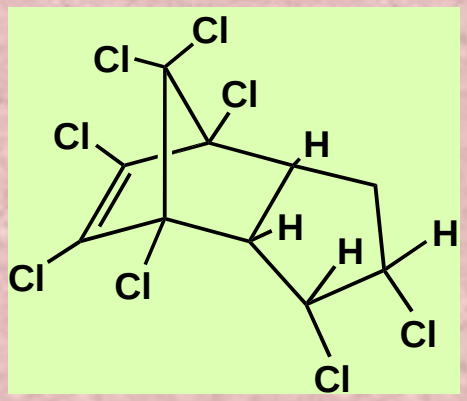
HCF_2Cl - Freon-22 (destroyed at lower altitudes)

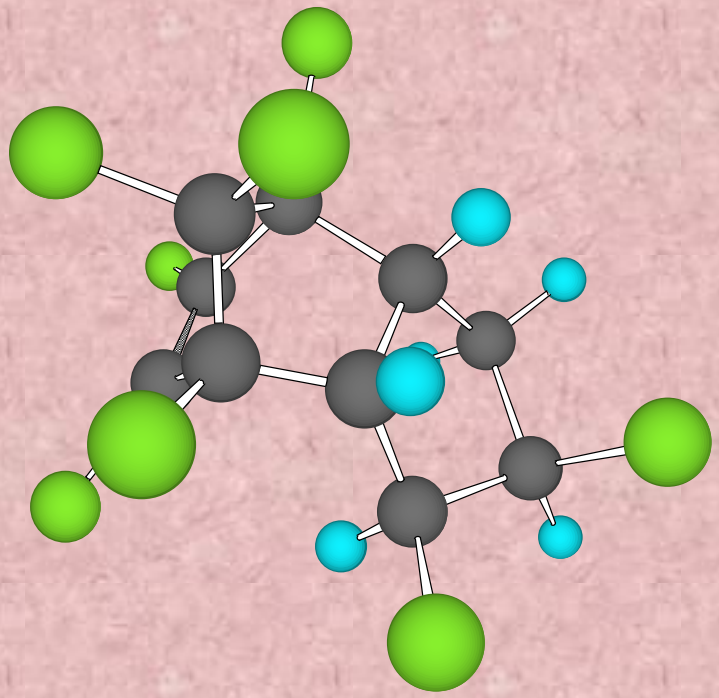
c. pesticides: DDT

- introduced 1939
- banned 1972 (Rachael Carson)

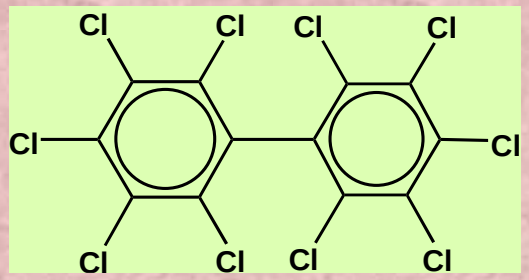


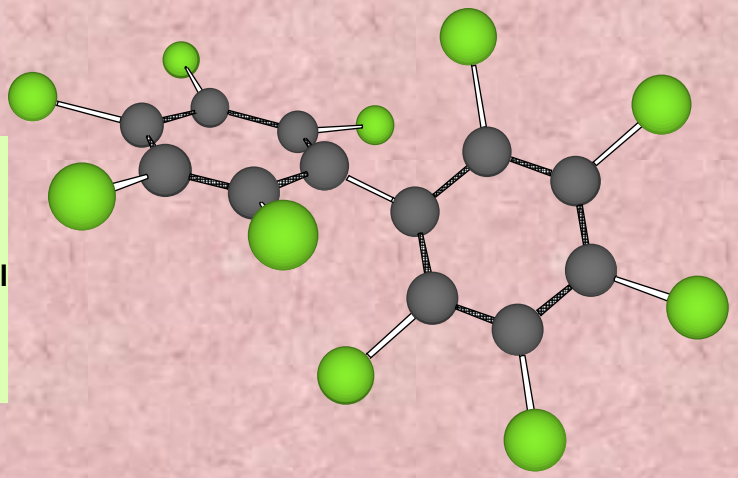






chlordane - termites
•banned 1995





capacitors, etc.
PCB (polychlo-rinated biphenyl)
•banned 1985

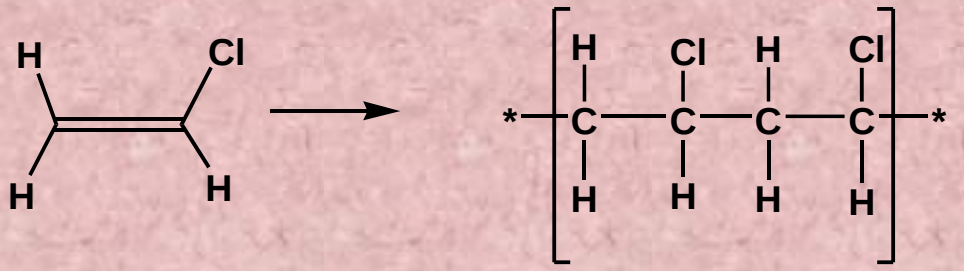
d. Anesthetics

$CHCl_3$ - chloroform carcinogenic

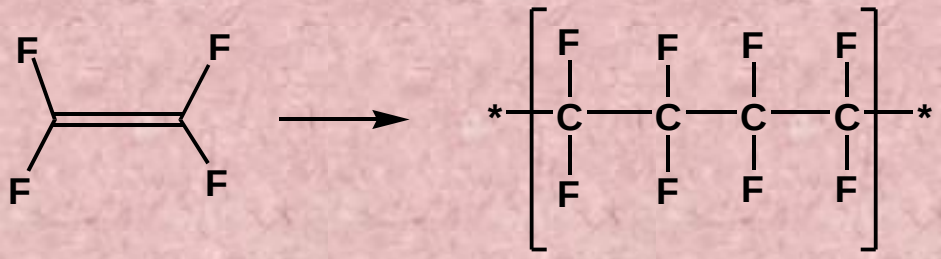
CH_3CH_2Cl - ethyl chloride topical use

$CF_3CHBr\text{-}Cl$ - halothane - general

e. polymers

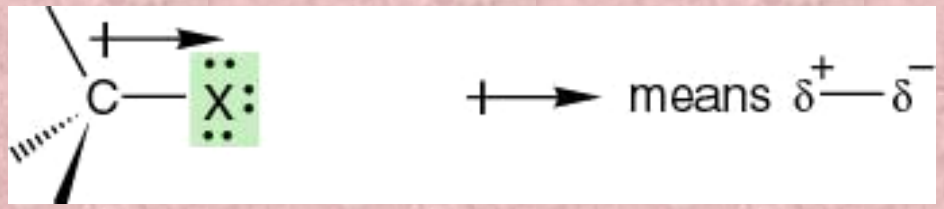


polyvinyl chloride (PVC)



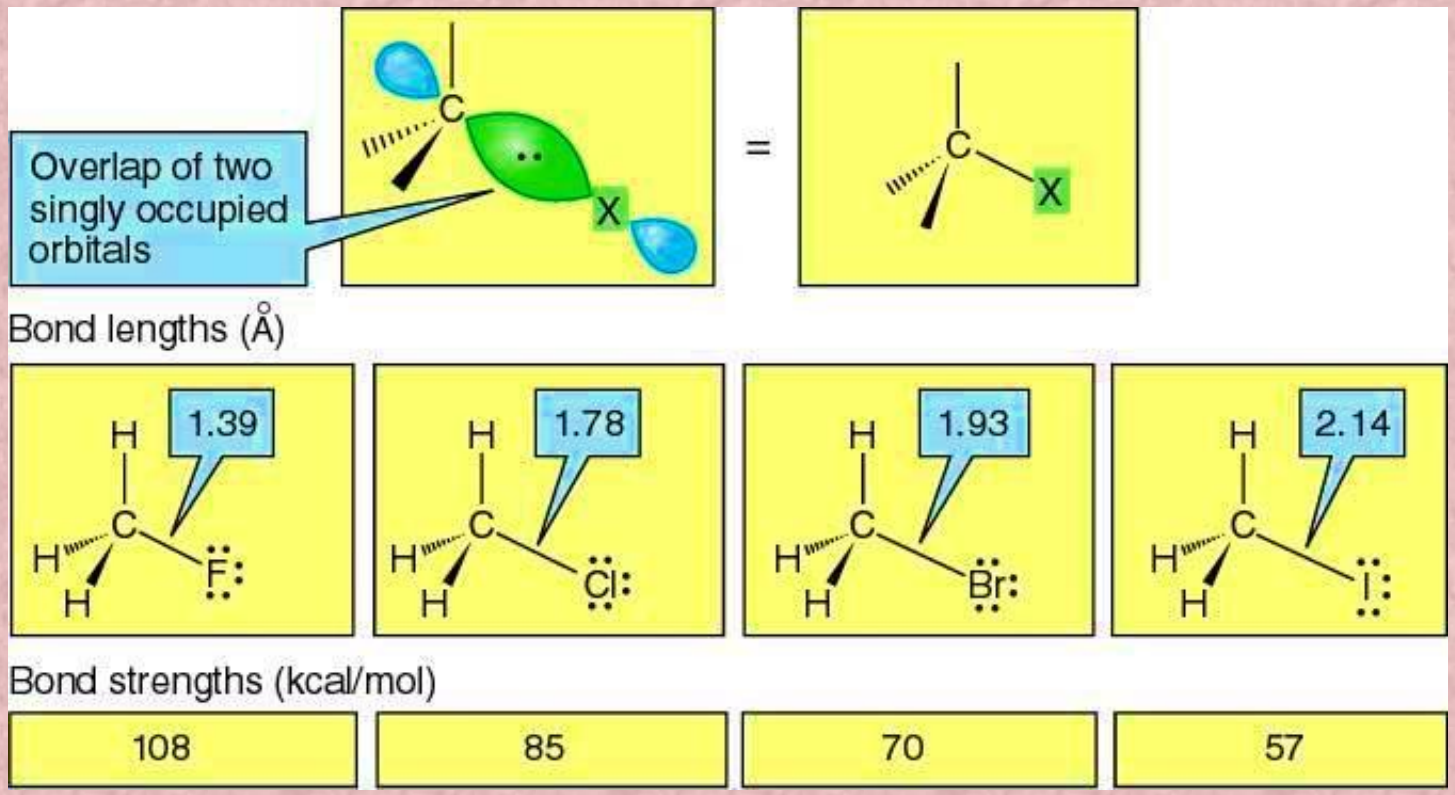
teflon

C. structure/properties



X = F
= Cl
= Br
= I

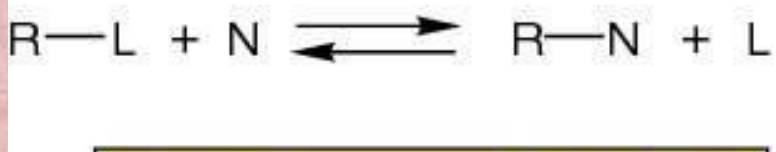
increasing electronegativity



Reactions of alkyl halides - **substitution**

1. general reaction

The general case



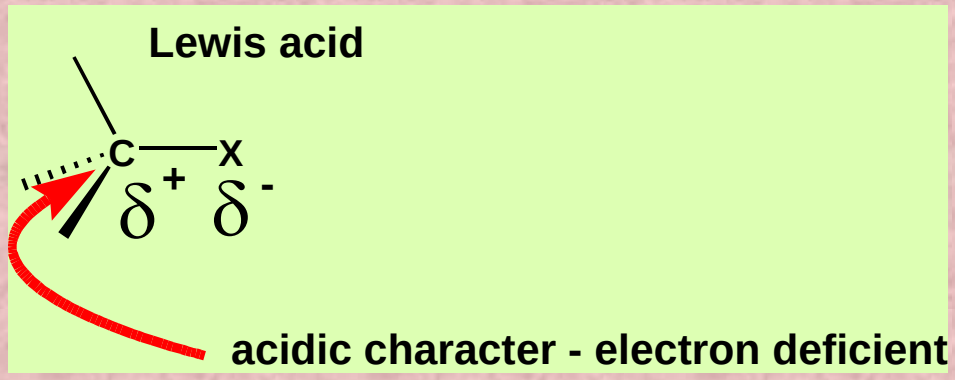
R =

H_3C Methyl group	$(CH_3)_2CH$ Isopropyl group
CH_3CH_2 Ethyl group	$(CH_3)_3C$ *tert*-Butyl group

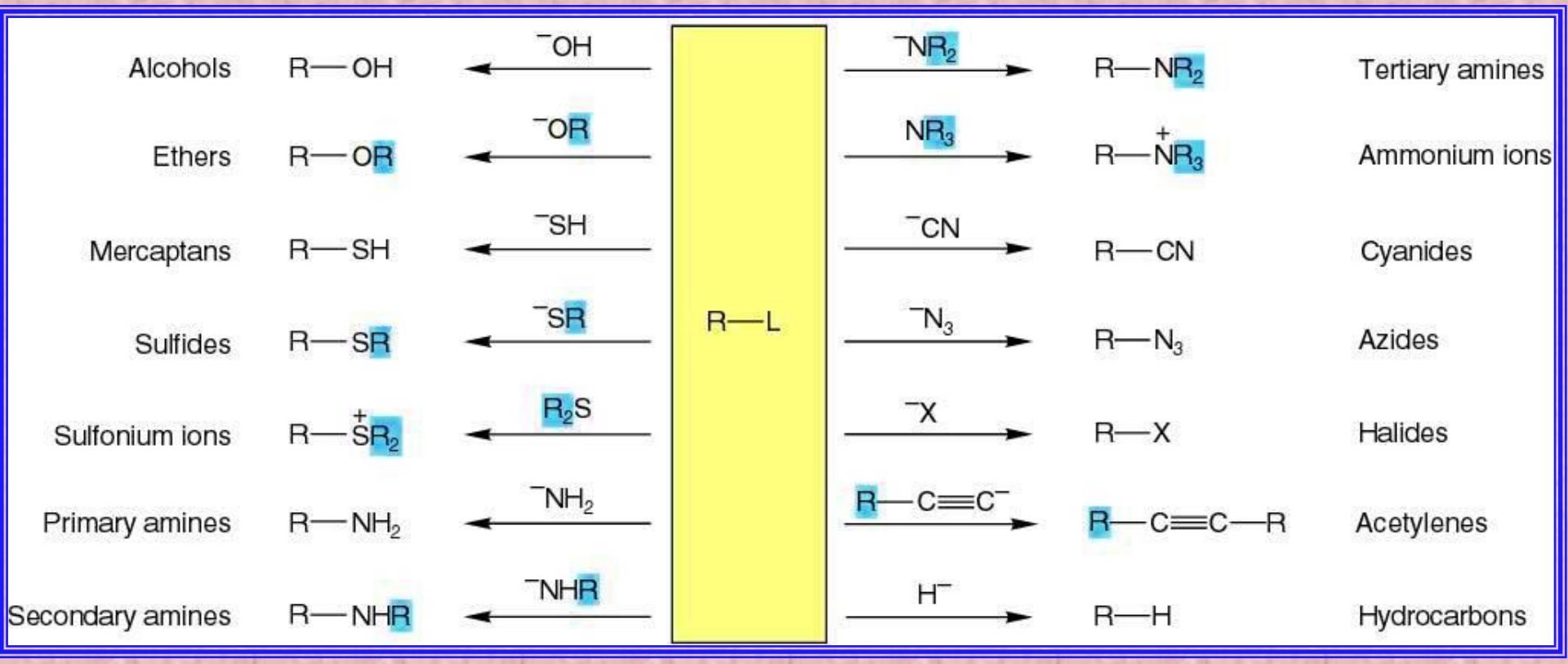
N = nucleophile - electron rich - Lewis base

R-L = electrophile - electron poor - Lewis acid

L = leaving group - must form a stable species (weak base e.g. X^-)

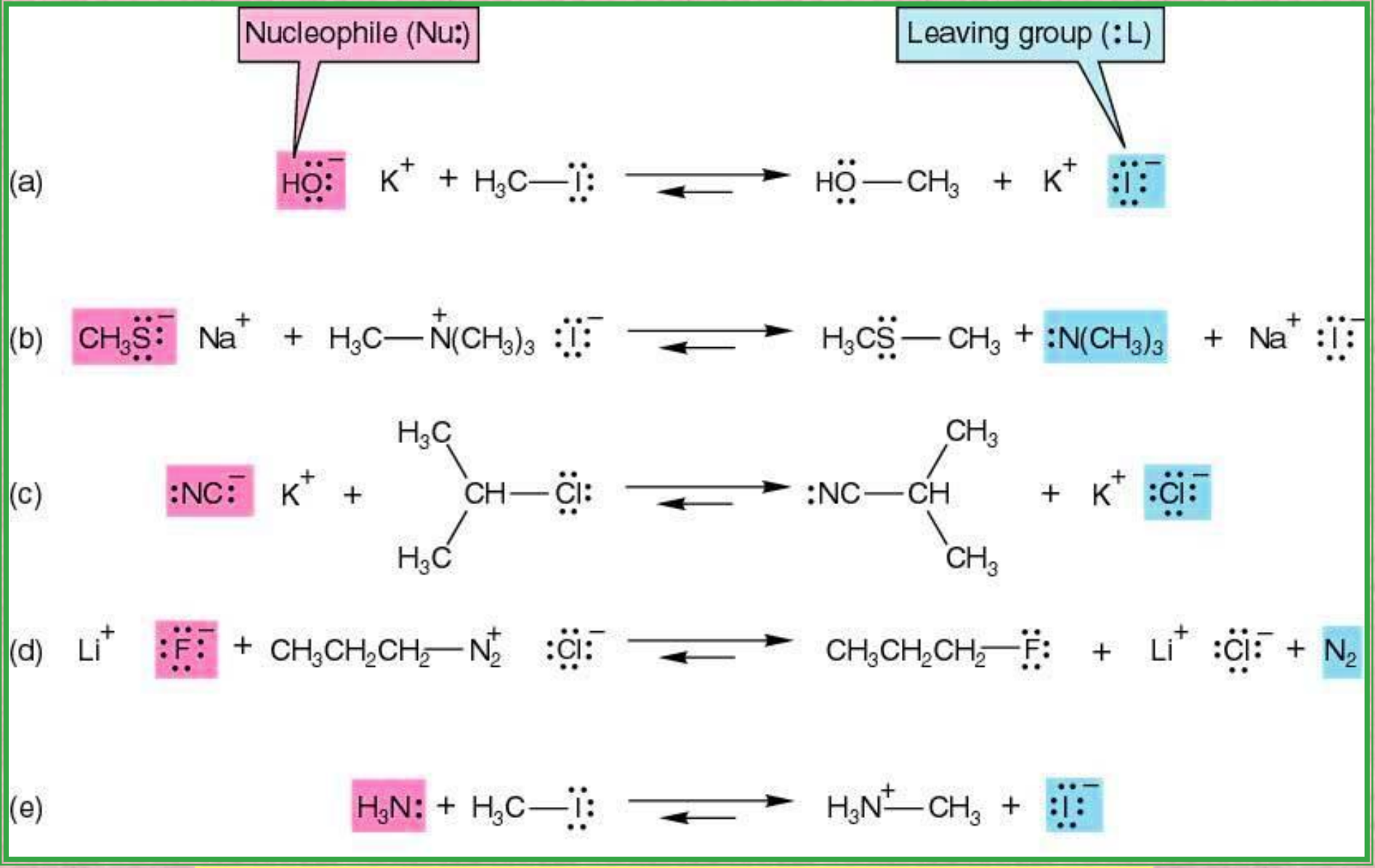


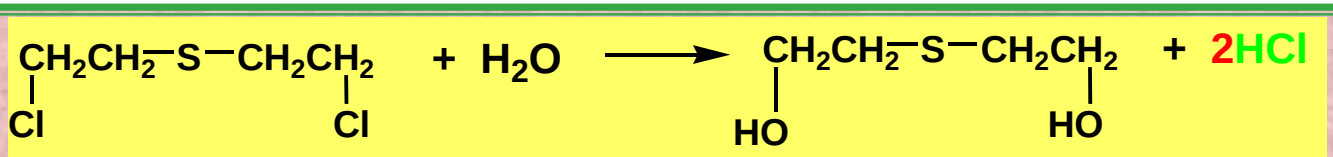
Reactions of alkyl halides - **substitution** general examples:



(L is not always X^- in these examples)

Reactions of alkyl halides - **substitution:** specific examples





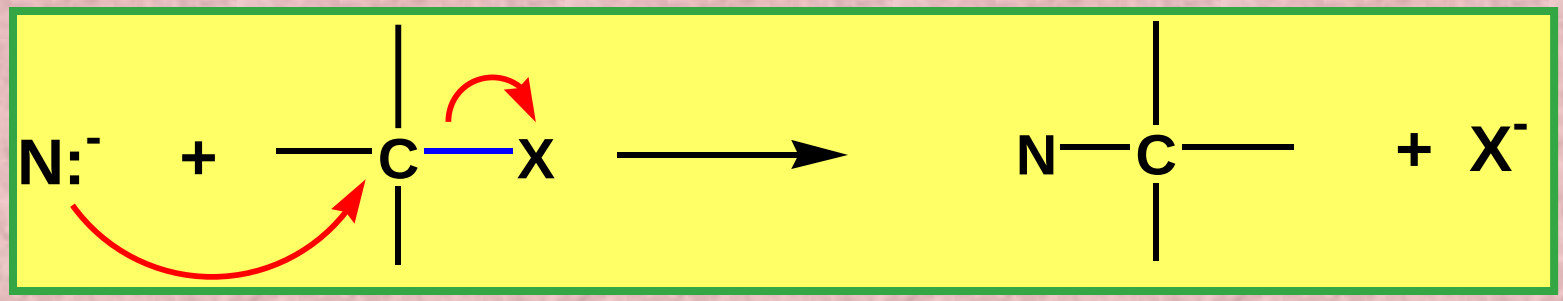
Reaction mechanism - there are two: First we will look at

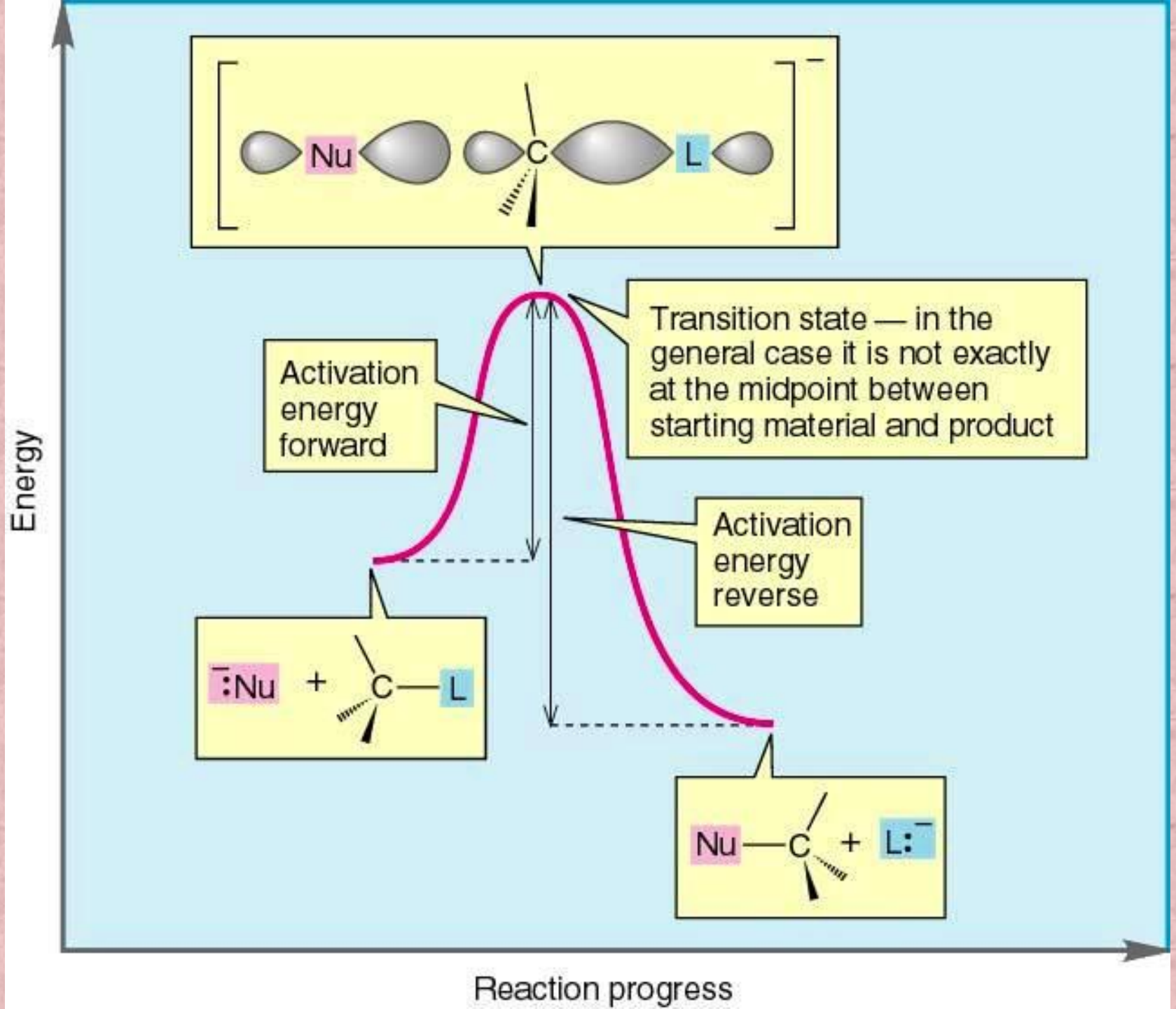
S_N2 - substitution nucleophilc bimolecular

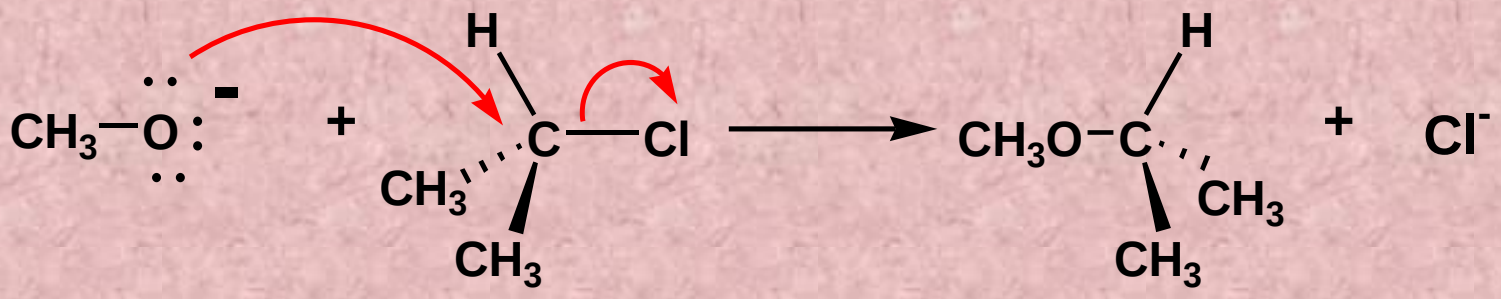
1. Rate law:

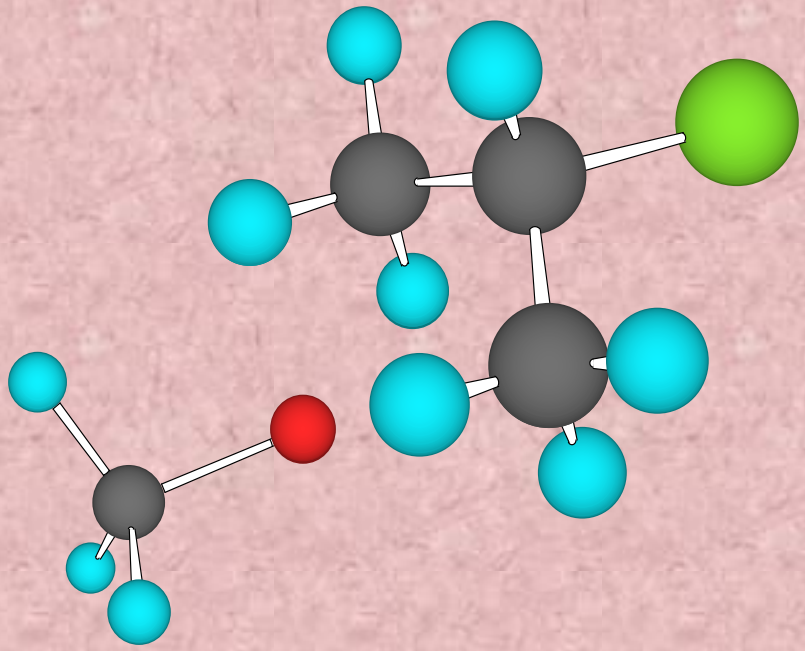
rate = k[R-L][N] ie dependent on both concen. of nucleophile and electrophile

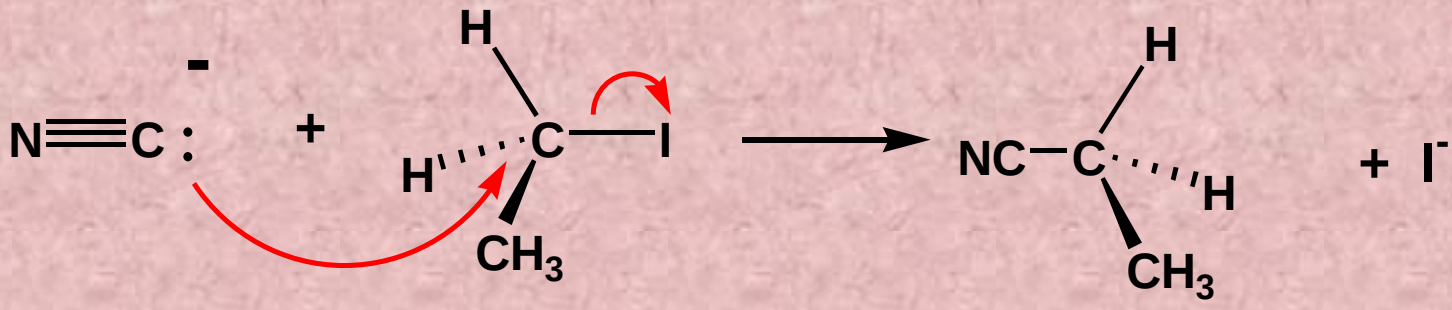
2. Mechanism - one step:



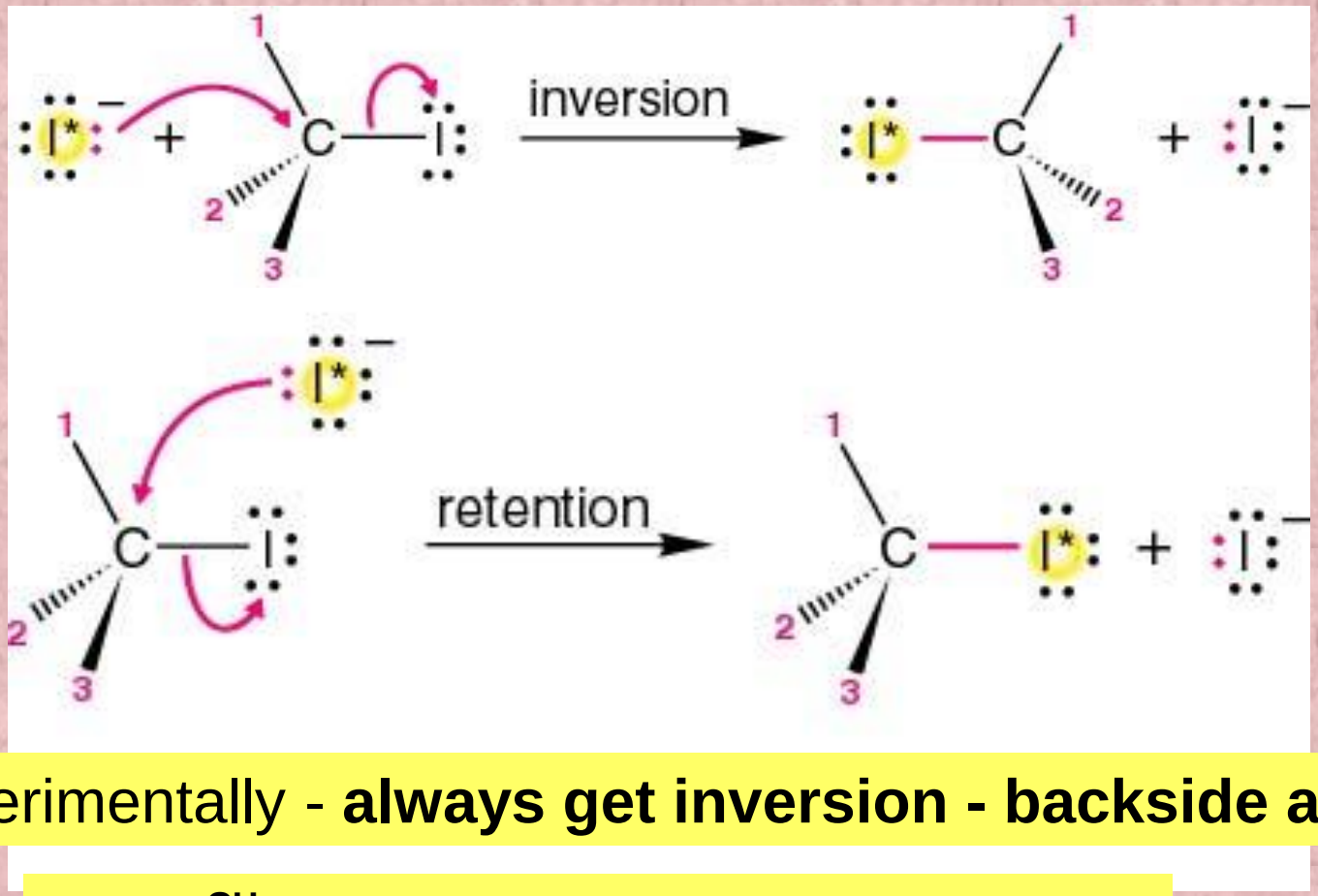

Nu
C
L
−
Transition state — in the general case it is not exactly at the midpoint between starting material and product
Activation energy forward
Activation energy reverse
:Nu
+
C
L
Nu
C
+
L:
Energy
Reaction progress


CH3—O:
-
+
H
C
Cl
CH3
CH3
CH3O—C
CH3
CH3
+
Cl-

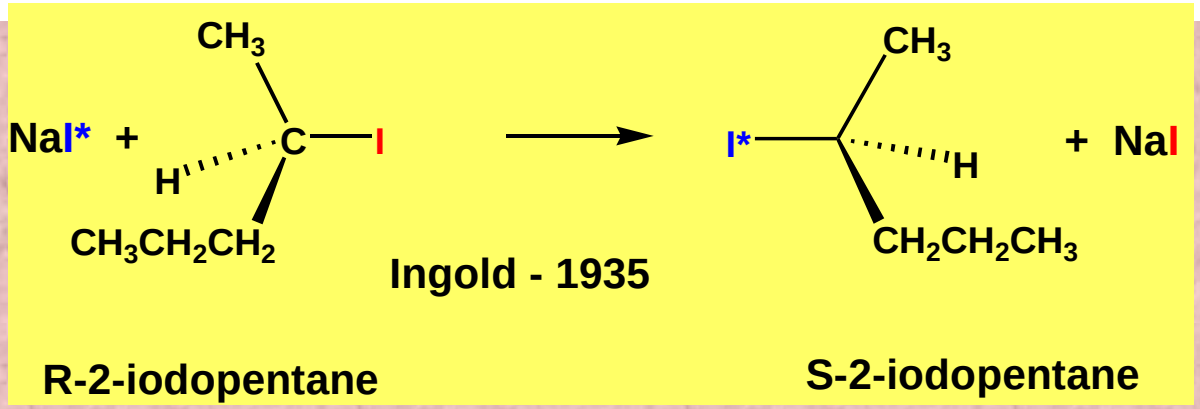



N≡C:
-
+
H
H
C
I
CH3
NC—C
H
H
CH3
+ I-

stereochemistry in S_N2 mechanism:



Experimentally - **always get inversion - backside attack**



Effect of nucleophile

The stronger the base - in general - the stronger the nucleophile.

Examples:

H_2O: versus $HO^{:-}$

$CH_3O^{:-}$ versus $HO^{:-}$

$H_2N^{:-}$ versus $HO^{:-}$

Basicity factors -

a. electronegativity of atom that contains the lone pair

b. inductive effects of substituents on lone pair

c. resonance effects - delocalization of lone pair

There is one major exception to this behaviour:

The size of the orbital and polarizability -

Nucleophilicity increases going from top to bottom row in Periodic Table.

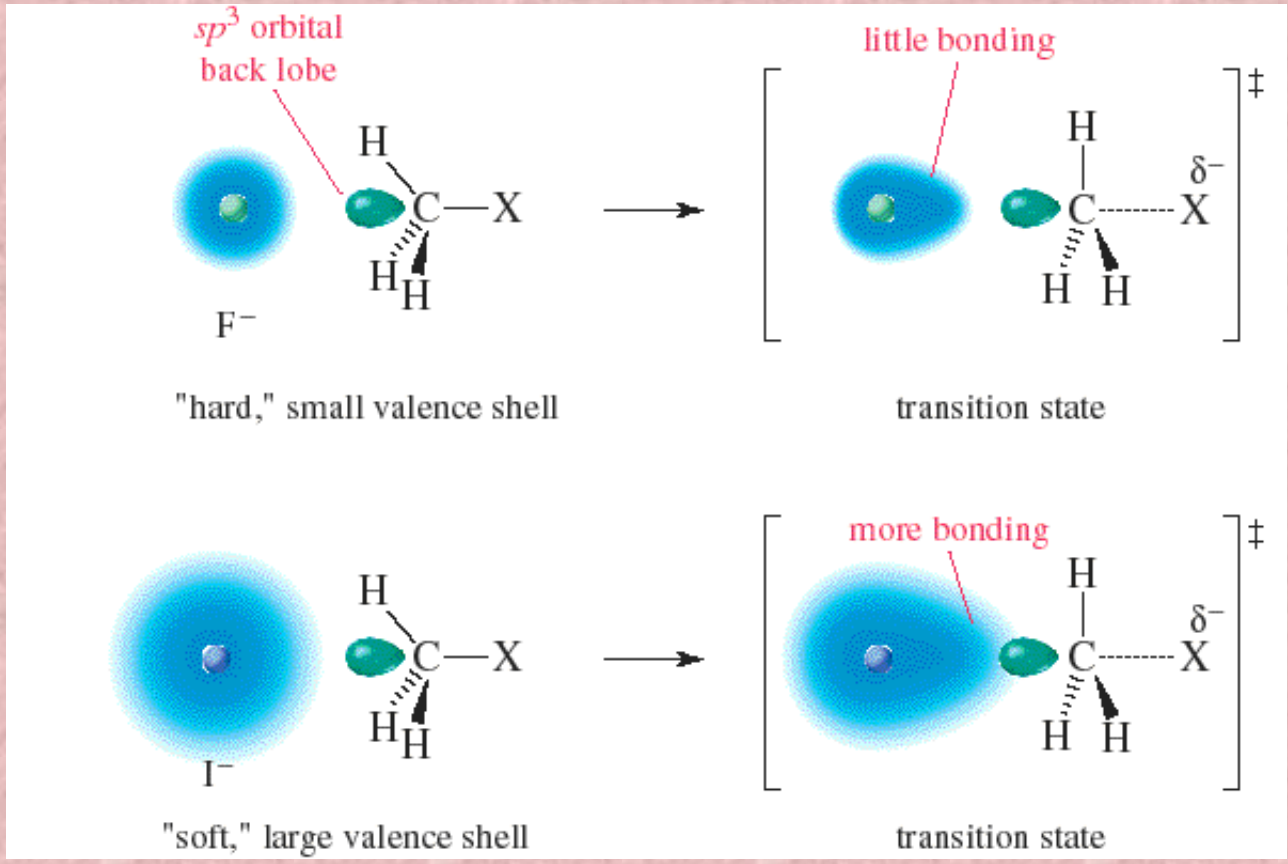
The size of the orbital and polarizability -

Nucleophilicity increases going from top to bottom row in Periodic Table.

$(CH_3CH_2)_2S > (CH_3CH_2)_2O$

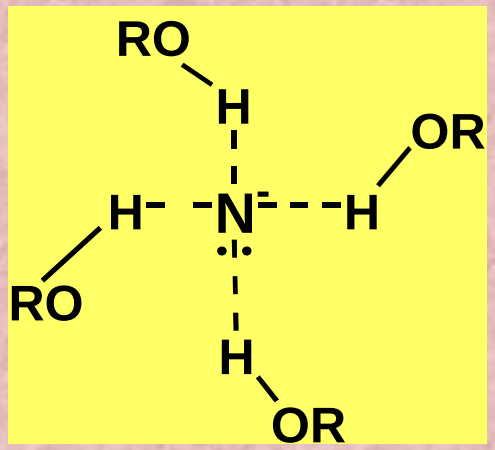
$(CH_3)_3P > (CH_3)_3N$

$I^- > Br^- > Cl^- > F^-$



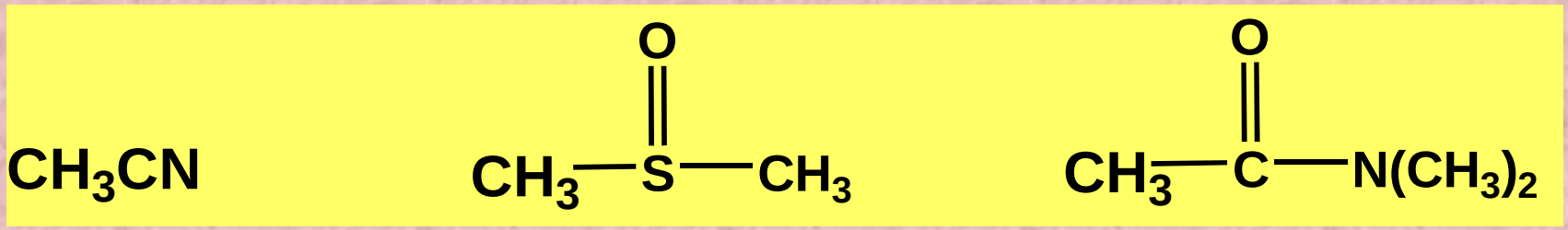
Solvent effects on nucleophilicity -
In general nucleophiles are polar or ionic molecules so we need a polar solvent to solvate them.

a. protic solvents, ie H_2O, ROH, etc.



Hydrogen bonding decreases nucleophilicity - particularily for small nucleophiles

b. polar, aprotic solvents - very high bp.



Acetonitrile DMSO DMF

drug delivery - rabbits

Leaving group effects:

The R-L bond should be as weak as possible, therefore, L should be as stable as possible.

In other words, L should have:

a. an electron withdrawing group or atom connected to L

b. a polarizable atom connected to R

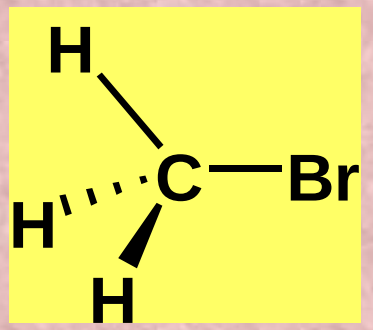
c. as weakly basic as possible

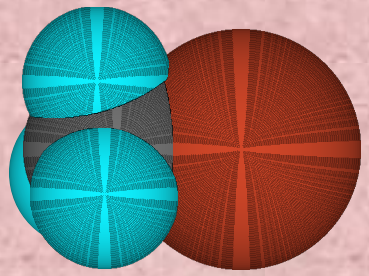
Acid	pK_a	Leaving Group	Name
		Good Leaving Groups	
HI	–10	^-I	Iodide
HBr	– 9	^-Br	Bromide
HCl	– 7	^-Cl	Chloride
$HOSO_2R$	– 6.5	$^-OSO_2R$	Sulfonate
H_3O^+	– 1.7	OH_2	Water
		Bad Leaving Groups	
HF	+ 3.2	^-F	Fluoride
H_2S	+ 7.0	^-SH	Thiolate
HCN	+ 9.2	^-CN	Cyanide
H_2O	+15.7	^-OH	Hydroxide
HOR	+16–18	^-OR	Alkoxide

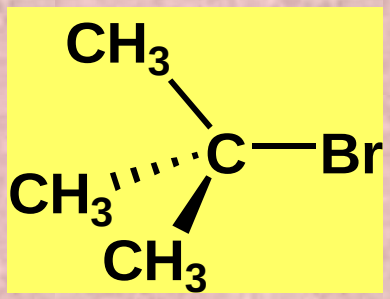
Effects in R - the alkyl group - primarily steric:

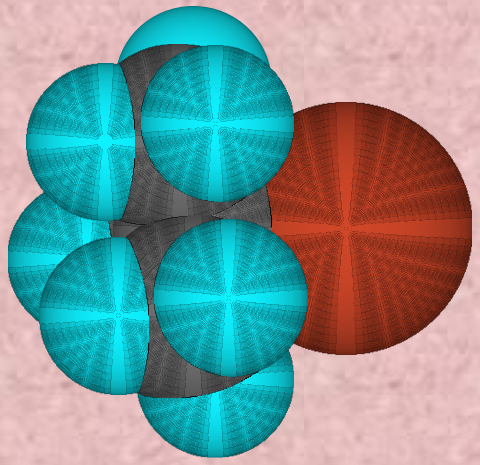
R	Relative rates
CH_3-	1.0
CH_3CH_2-	0.033
$CH_3CH_2CH_2$-	0.013
$(CH_3)_2CH$-	8.3×10^{-4}
$(CH_3)_3CCH_2$-	2×10^{-7}
$(CH_3)_3C$-	$<<10^{-7}$

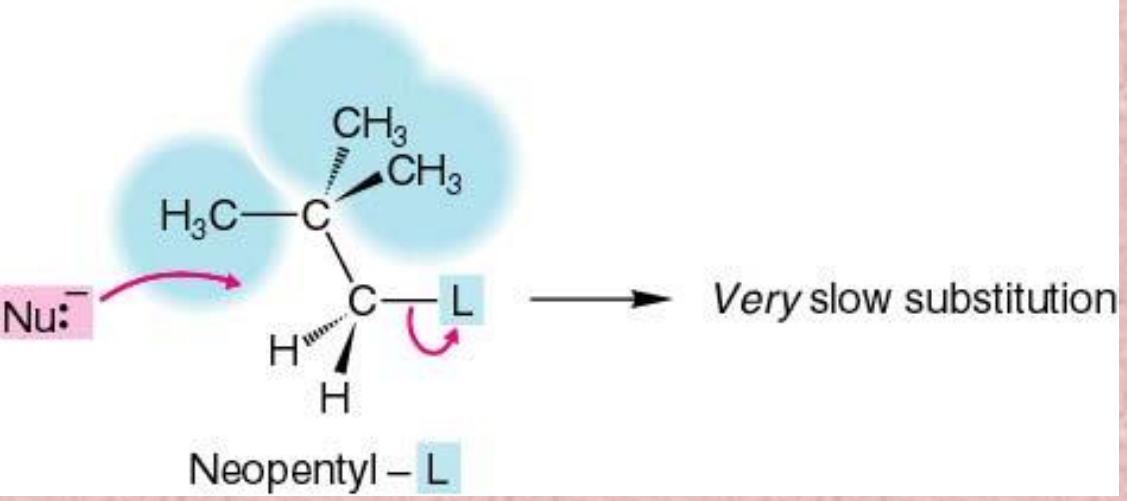
Space-filling model

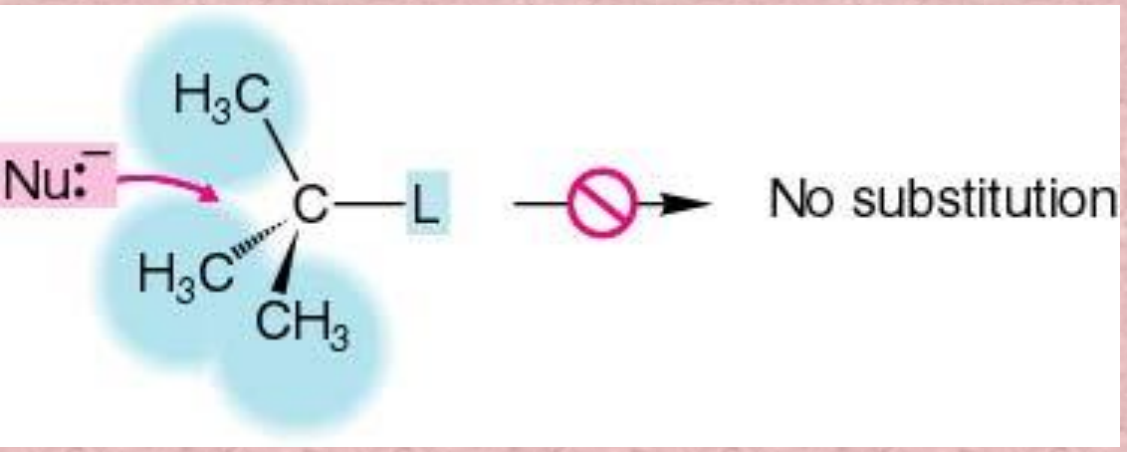


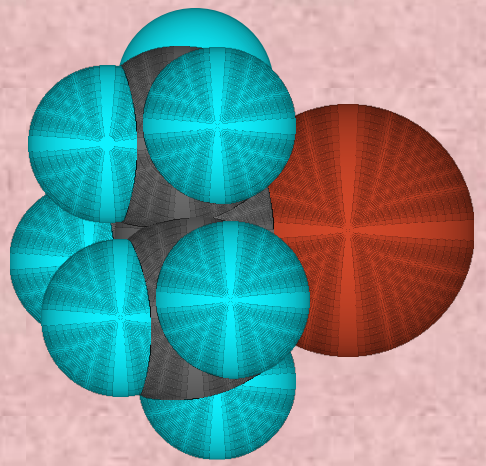












So for any R-L compound, the relative rates of S_N2:

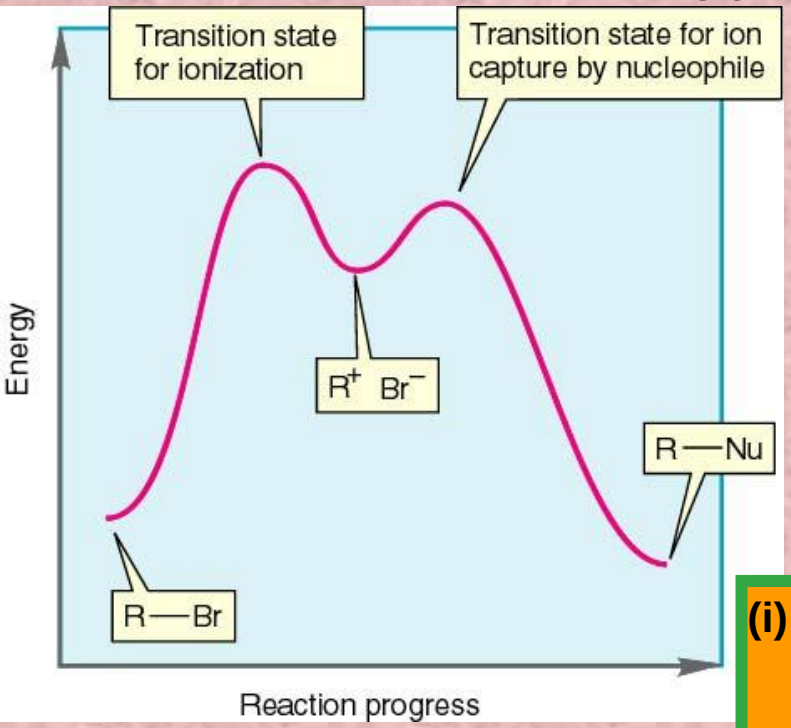
CH_3- > 1° > 2° > 3°

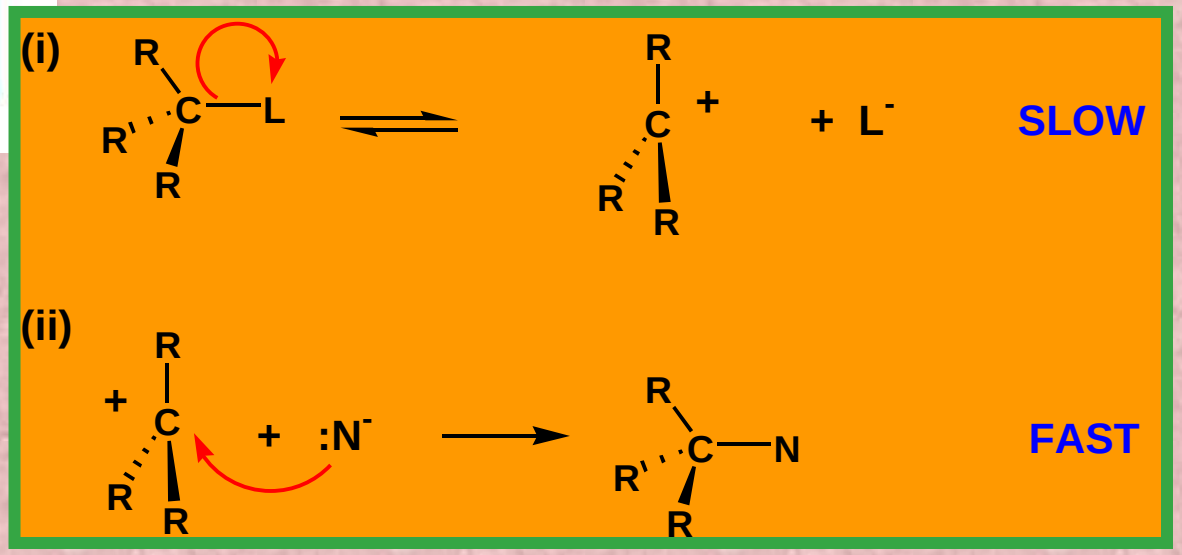
S_N1 - substitution nucleophilic unimolecular

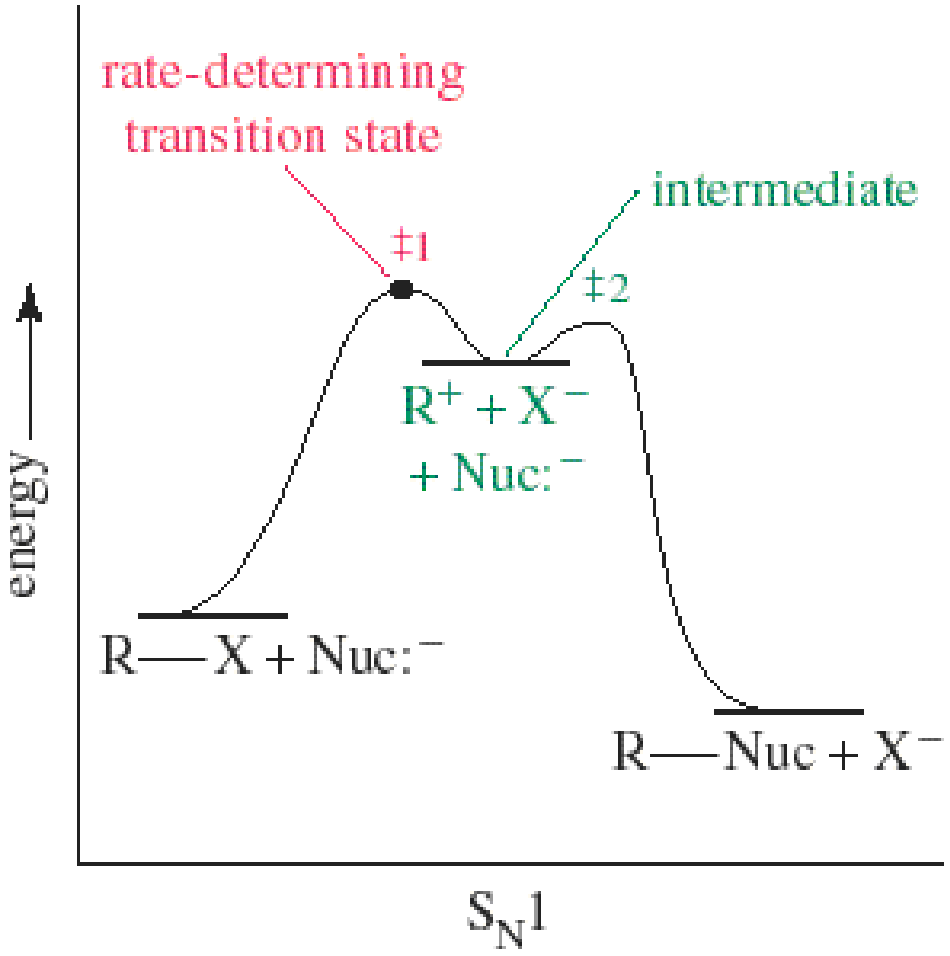
1. rate law:

rate = k[R-L] not dependent upon the conc. of N:!

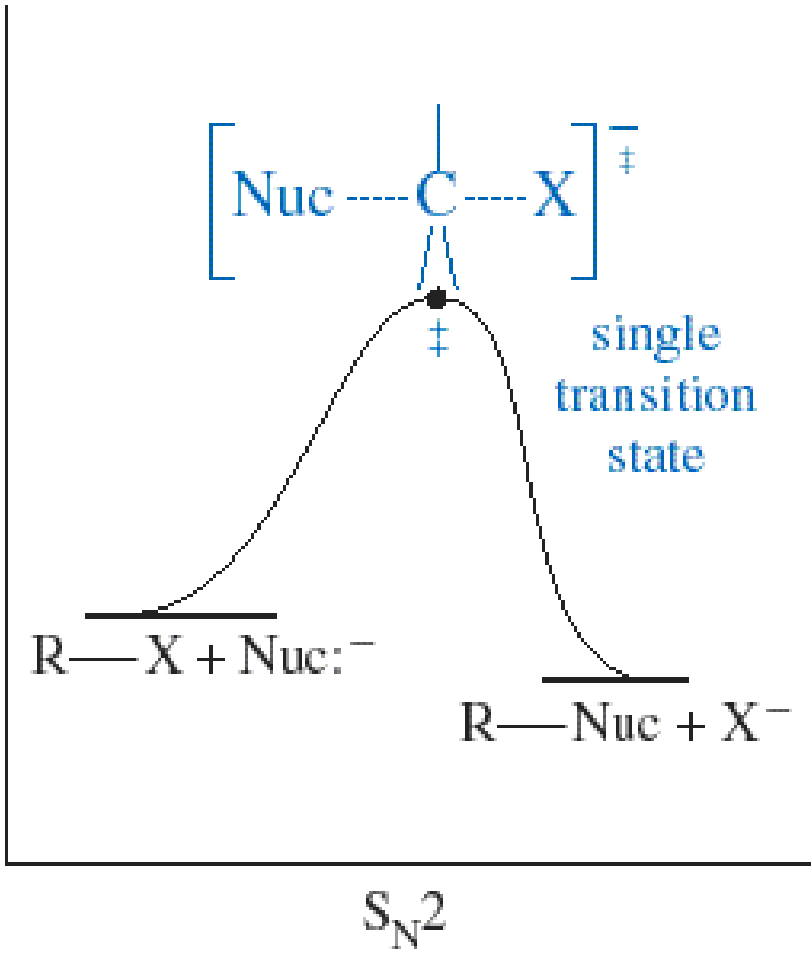
2. mechanism - two steps:





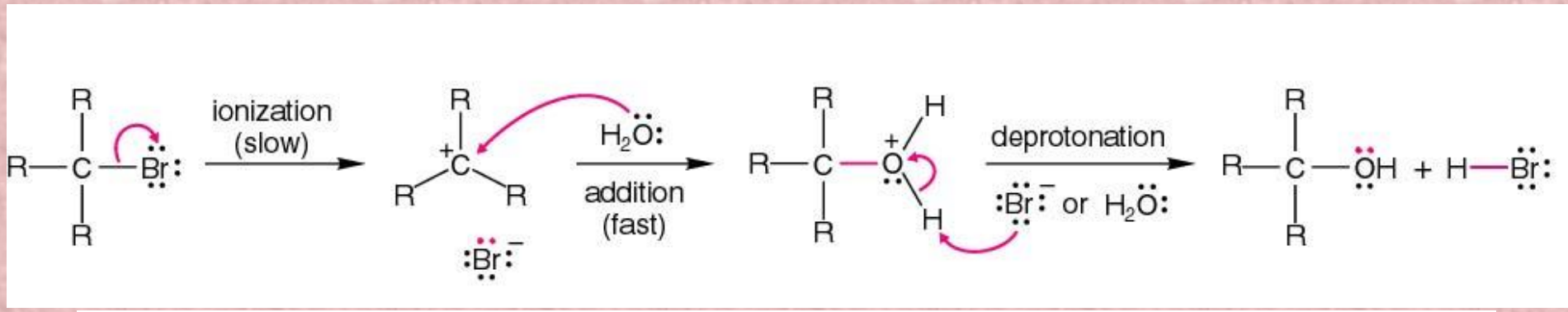

rate-determining
transition state
intermediate
‡1
‡2
energy
R⁺ + X⁻
+ Nuc:⁻
R—X + Nuc:⁻
R—Nuc + X⁻

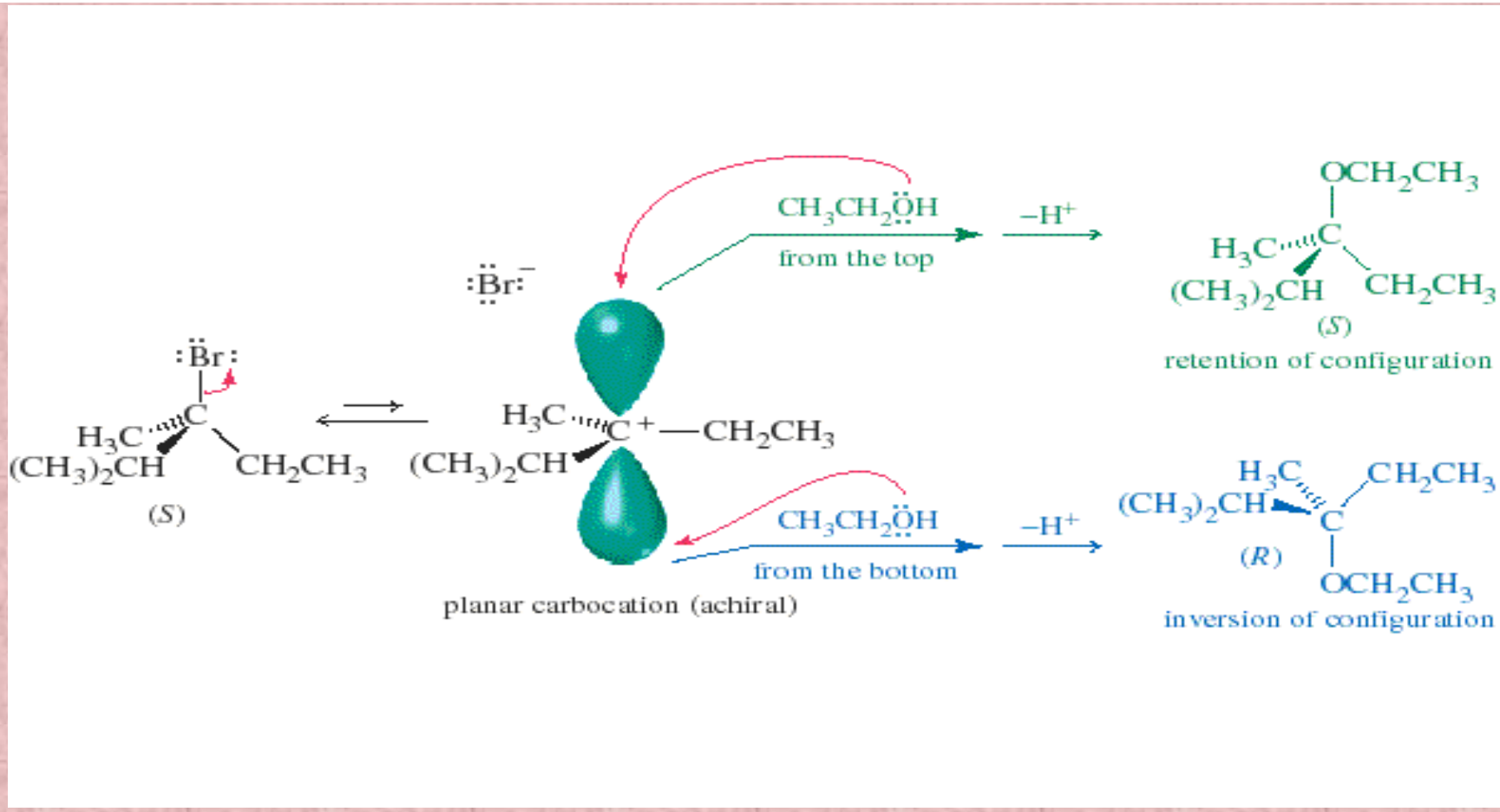
S_N1


Nuc ----- C ----- X
‡
single
transition
state
R—X + Nuc:⁻
R—Nuc + X⁻

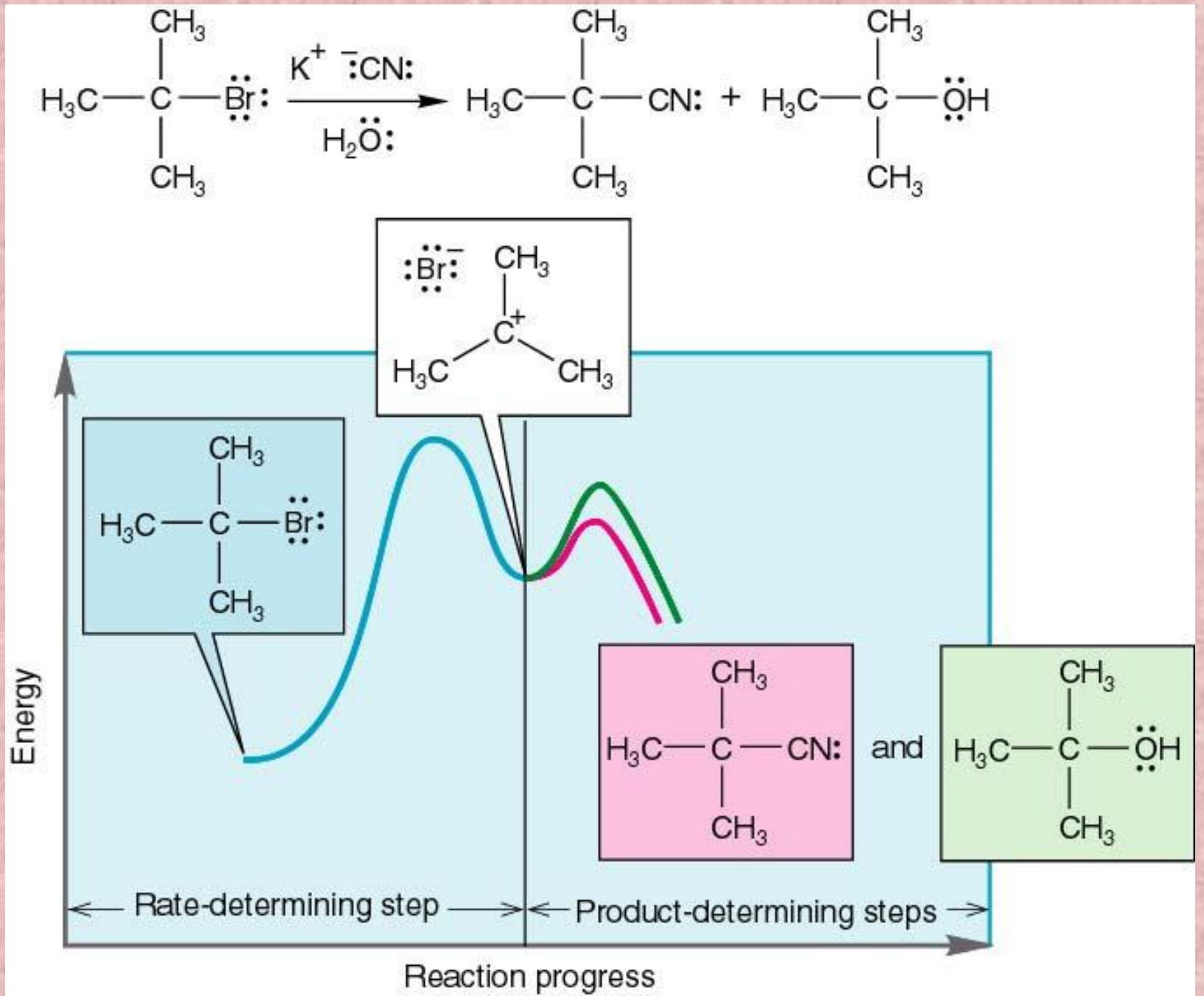
S_N2

Stereochemistry - racemization

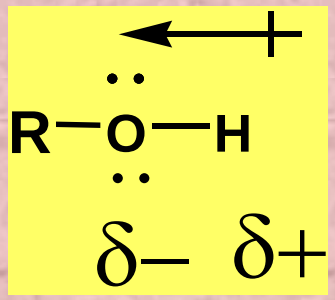


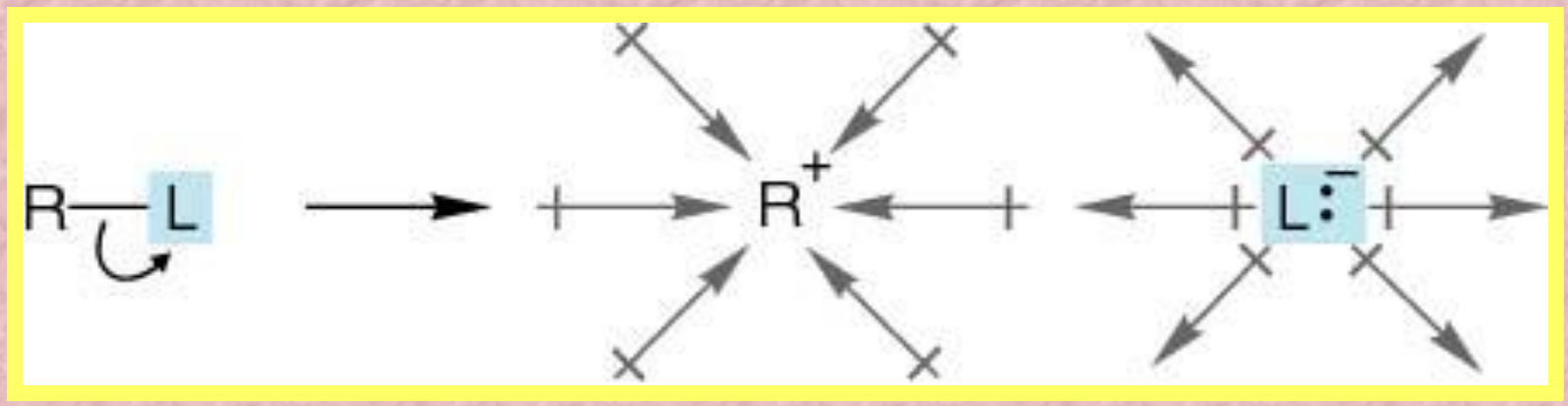


Effect of nucleophiles: to a first approximation - **none**



Solvents - we need a very polar solvent to stabilize the carbocation - water and alcohols are good





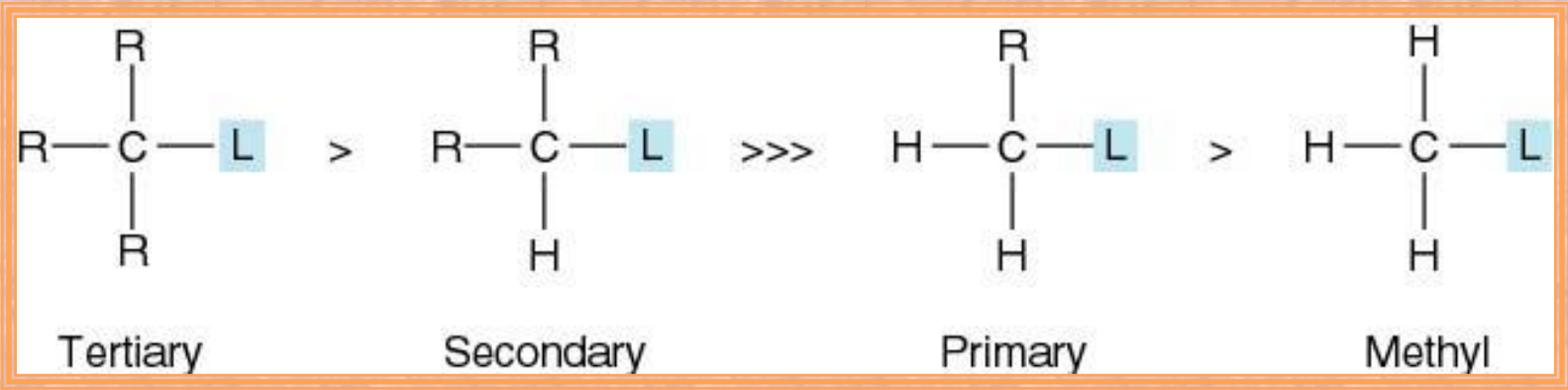
Leaving group effects - same as for S_N2 (weak R-L, stable L^-)

Effects in the alkyl group, R

primarily determined by the stability of the carbocation, R^+.

- R^+ is unstable - therefore, endothermic step
  - late transition state resembles R^+
  - stabilize R^+, stabilize transition state, faster reaction
  - destabilize R^+, destabilize transition state, slower reaction

Hammond principle

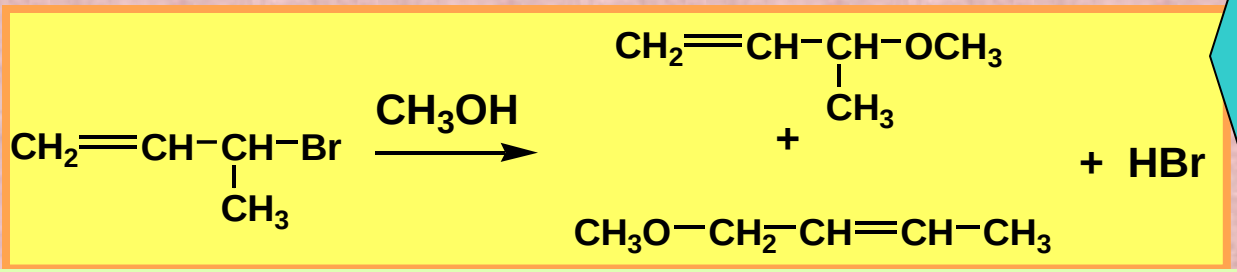


Steric argument: R-L = sp^3 but R^+ sp^2 hybridized.

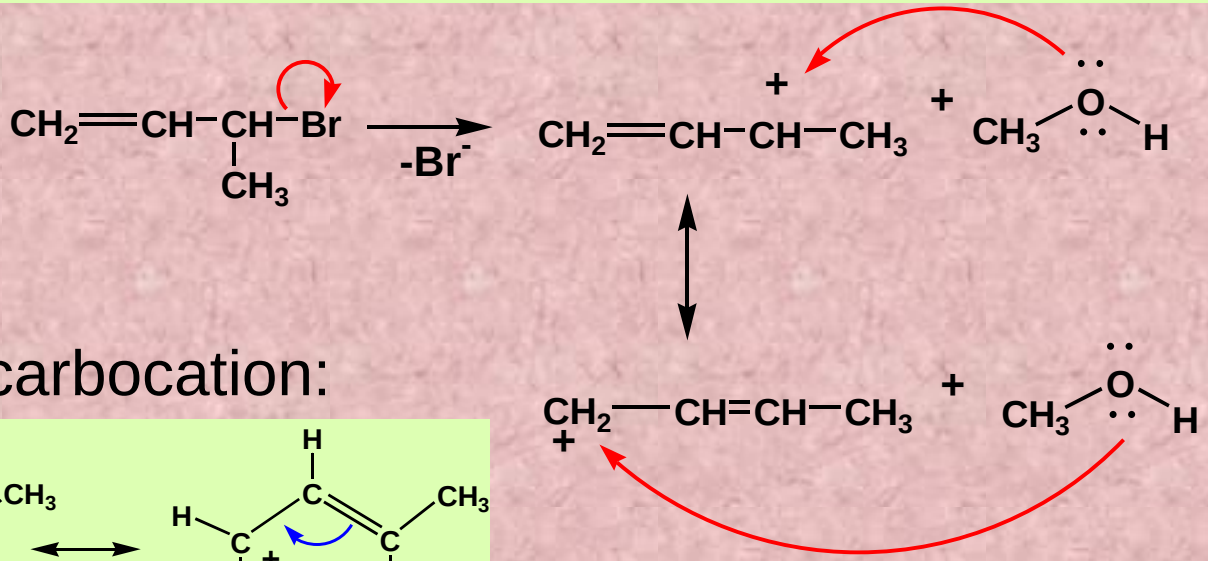
Electronic argument:

Recall hyperconjugation and resonance

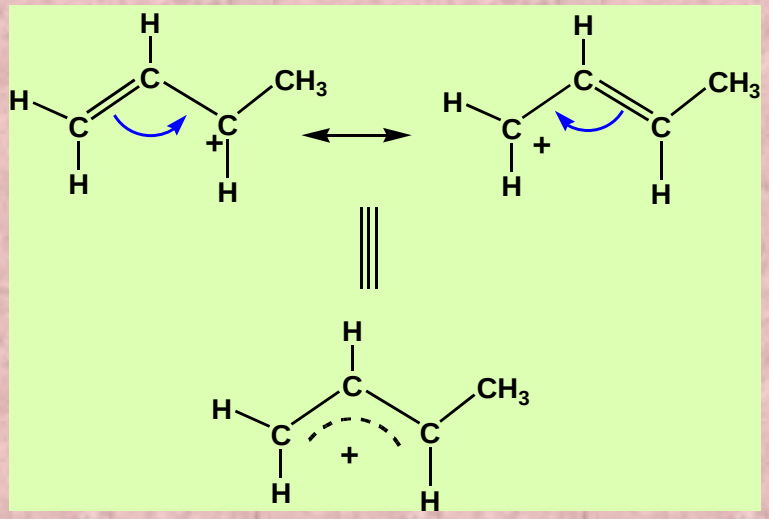
A special case - allylic substitution:



mechanism - consistent with carbocation intermediate:

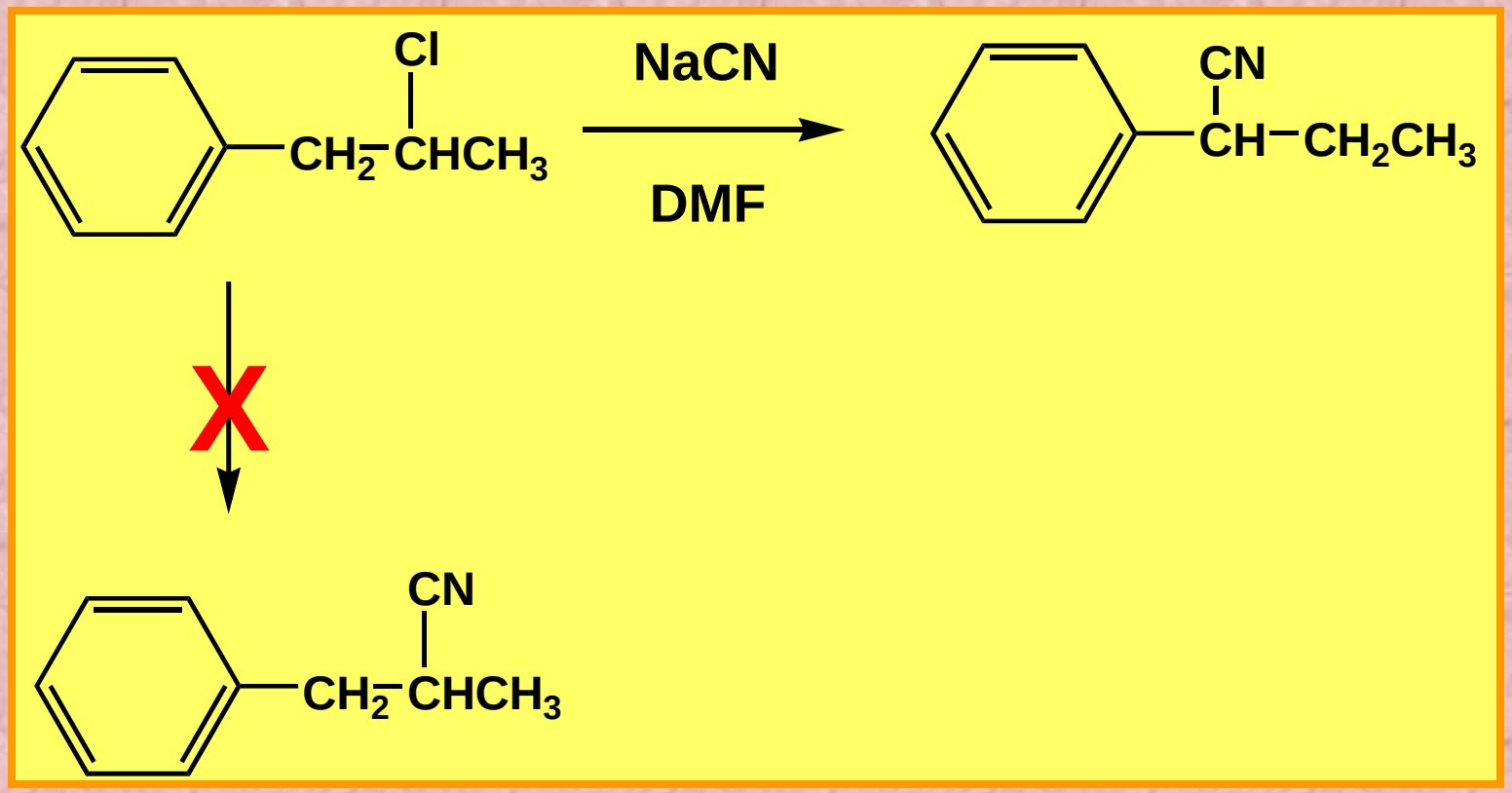


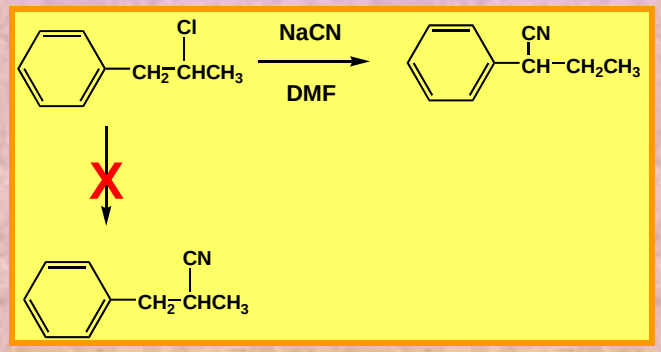
allyl carbocation:



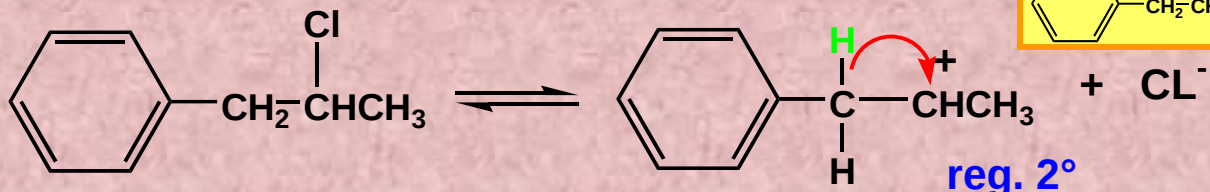
8. Rearrangements from a carbocation -
Primarily a 1,2-H shift to form a more stable carbocation.

Another mystery!!



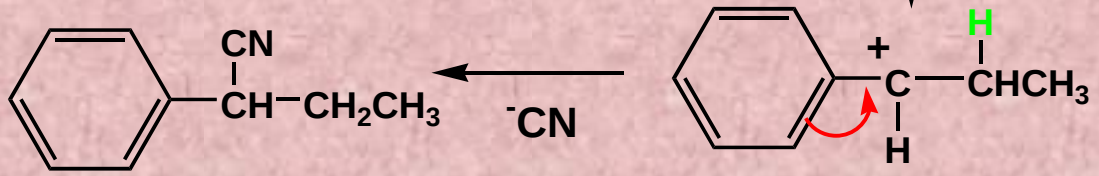


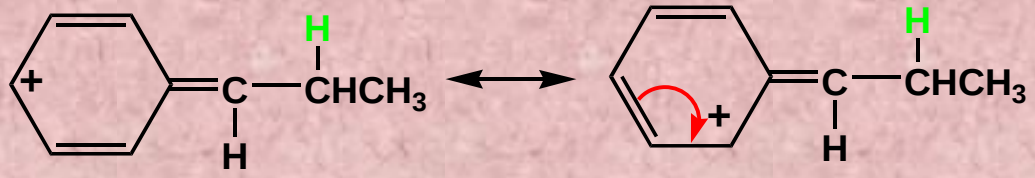
mechanism:



reg. 2° carbocation

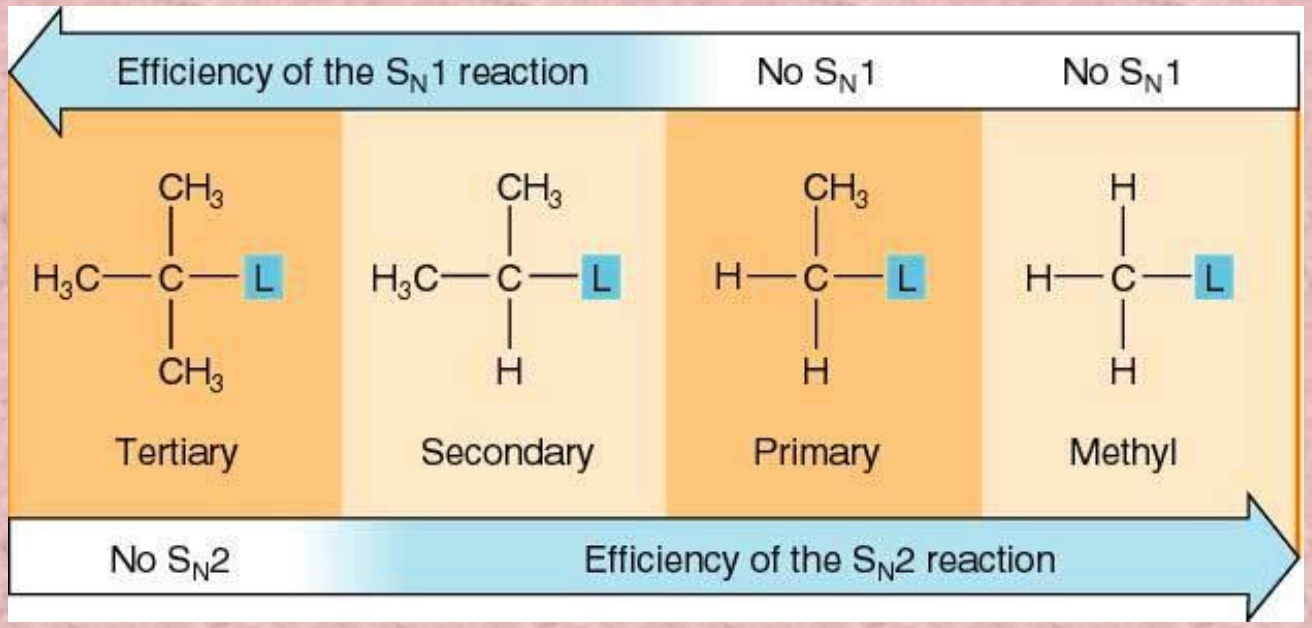
1,2 -H shift





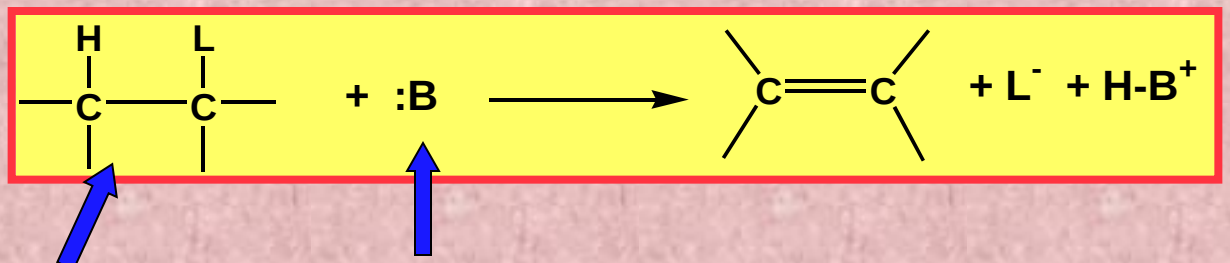
benzyl carbocation - stabilized by resonance

9. Difference between S_N1 and S_N2 - **PRIMARILY** the structure of R



- solvent polarity
- strength of R-L bond

H. Elimination reactions - general reaction scheme:



acid

base

L = leaving group

B = base

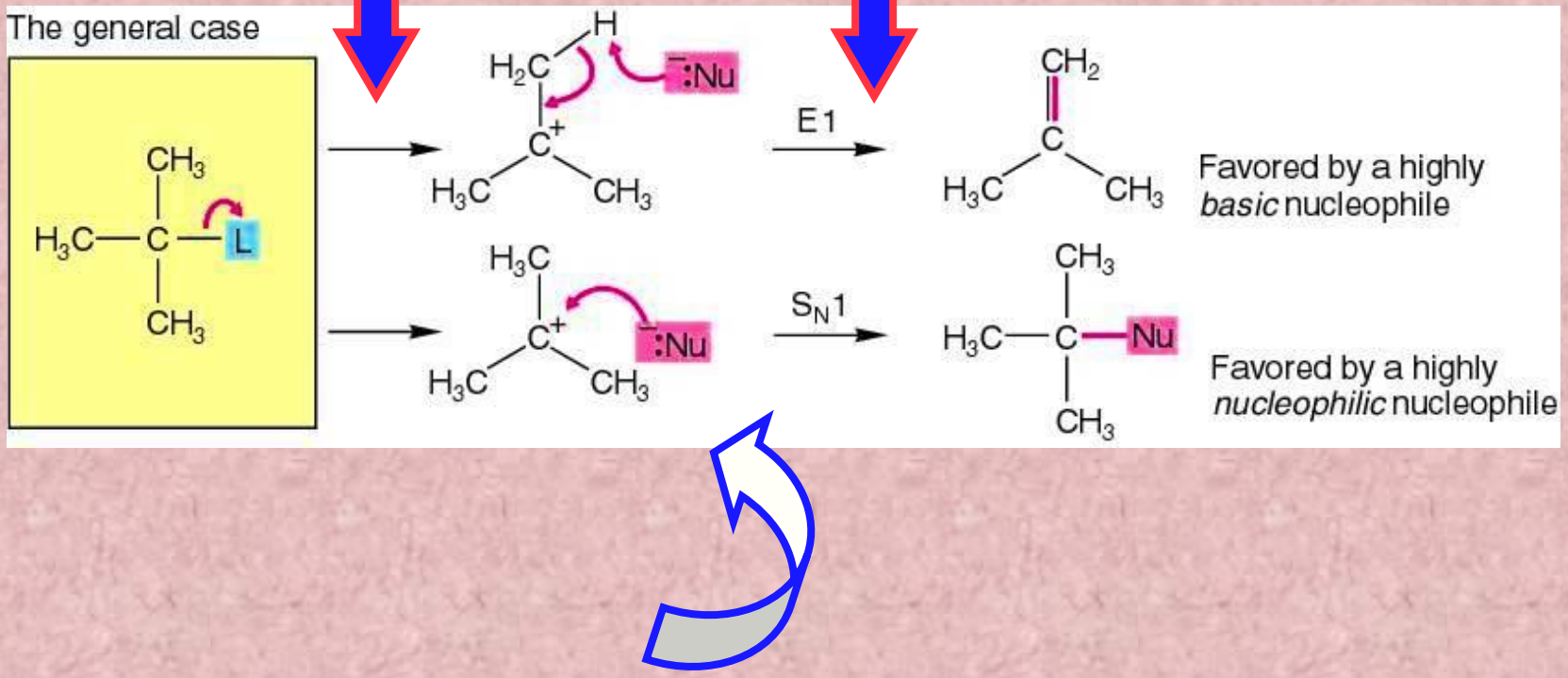
There are actually three mechanisms for this reaction

I. E1 - elimination unimolecular - proceeds just like S_N1- first step forms carbocation - -

1. mechanism:

rate determining slow step

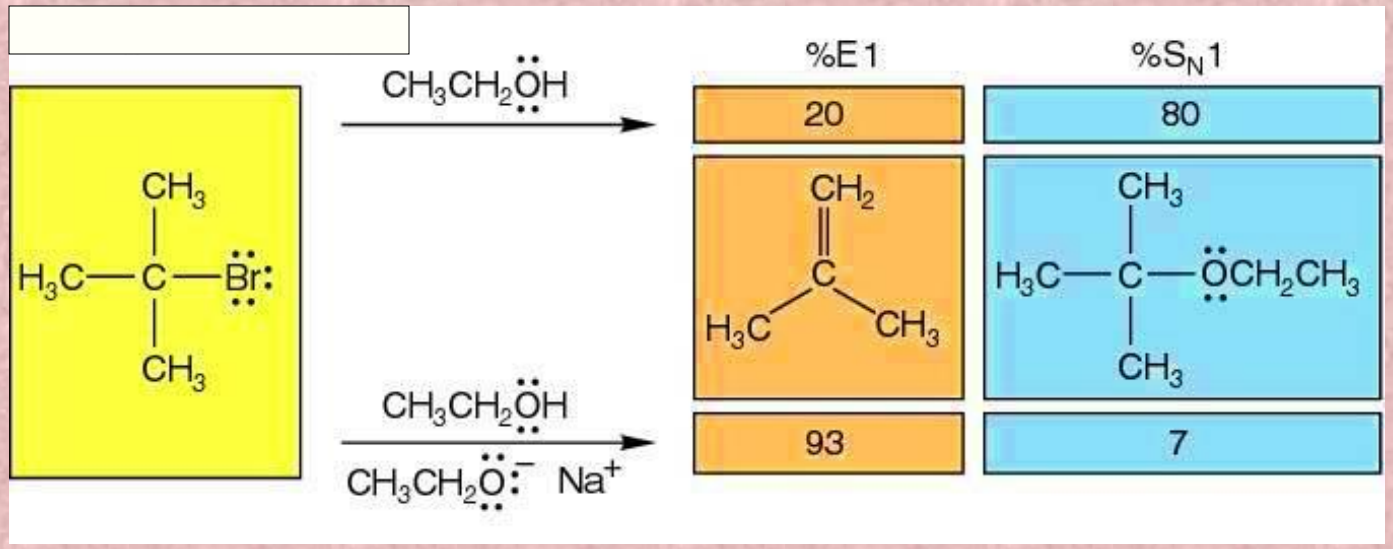
fast step



Note: potential competition with S_N1 reaction

Nucleophiles tend to be less basic.
Nucleophilicity refers to "how much" a reactant wants to "find" a positive charge. In other words, it measures the instability of the reactant's negative charge.
Basicity refers to "how much" a reactant wants to "find" a Hydrogen ion.
In both of these, the underlying drive is the same--both the base and the nucleophile want to stabilize their negative charge with a positive one.
So, the more unstable the negative charge of a reactant is, the higher its nucleophilicity AND its basicity.
The defining difference, then, is how a reactant behaves in the presence of a substrate that contains an electrophile or an abstractable hydrogen
A strong base will have such a great thermodynamic instability that it will attack a protic hydrogen
A good nucleophile, then, is not as basic and is more likely to be sterically unhindered.
Consider CN-. It will tend to act as a nucleophile and attack an electrophile
A reactant can be a good nucleophile and a good base and act as either.
Consider HO- or hydroxide. Depending on the conditions, it can act as a base and turn into water, or it can attack an electrophile in an SN_2 fashion
Consider Br- which is a base and a good nucleophile, It will tend to act in an SN2 fashion
As you can see it is very nuanced, and you have to consider the whole reaction when determining nucleophilicity and basicity.

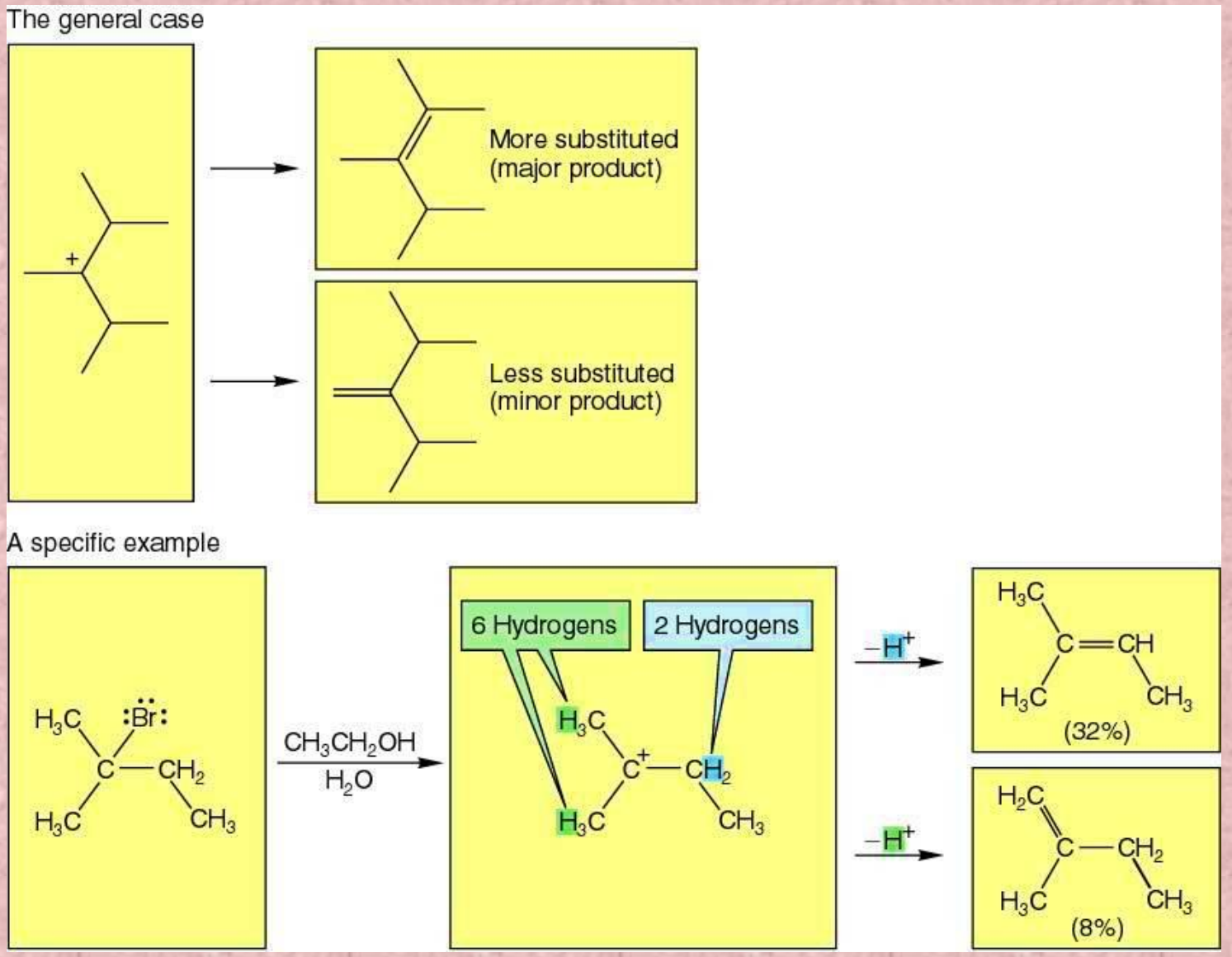
In **GENERAL** E1 is favored by a strong base, e.g.



2. orientation - generally follows

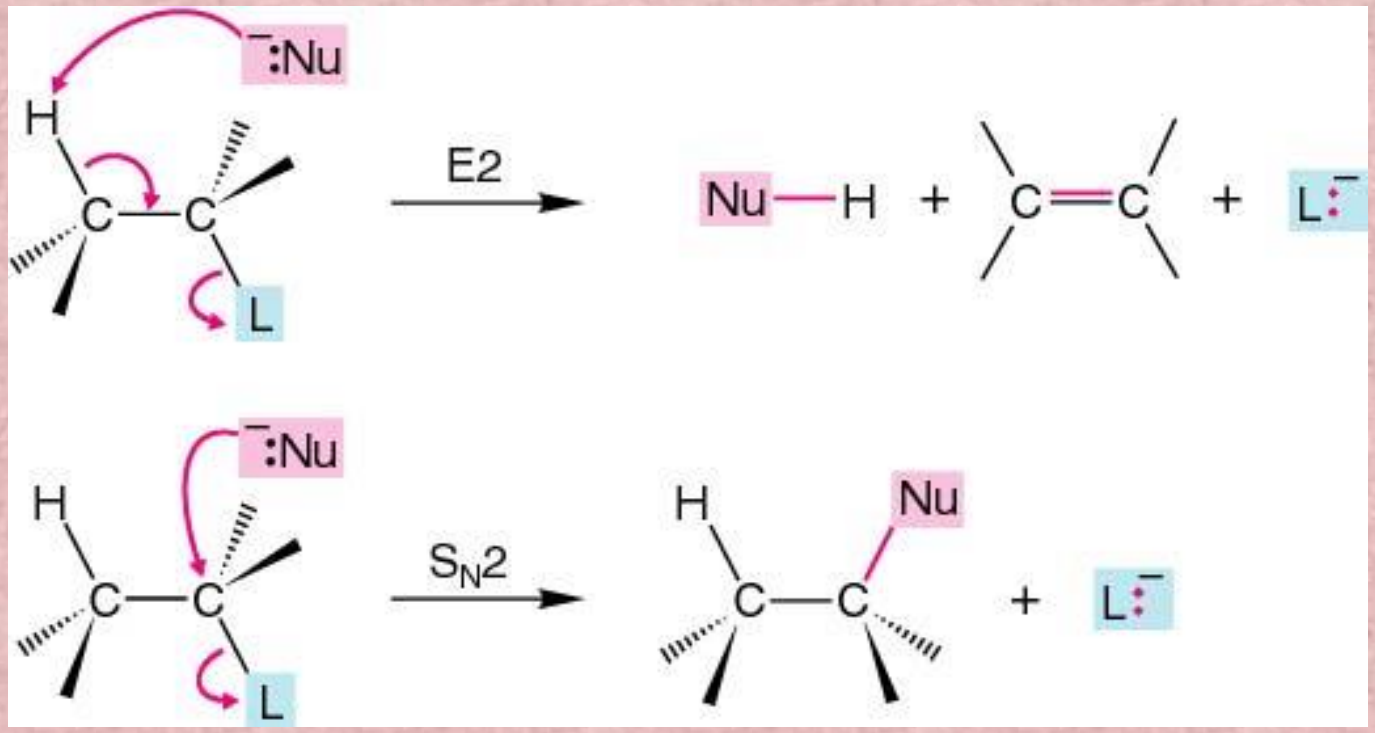
Saytzeff rule -

the most substituted(most stable) olefin is formed

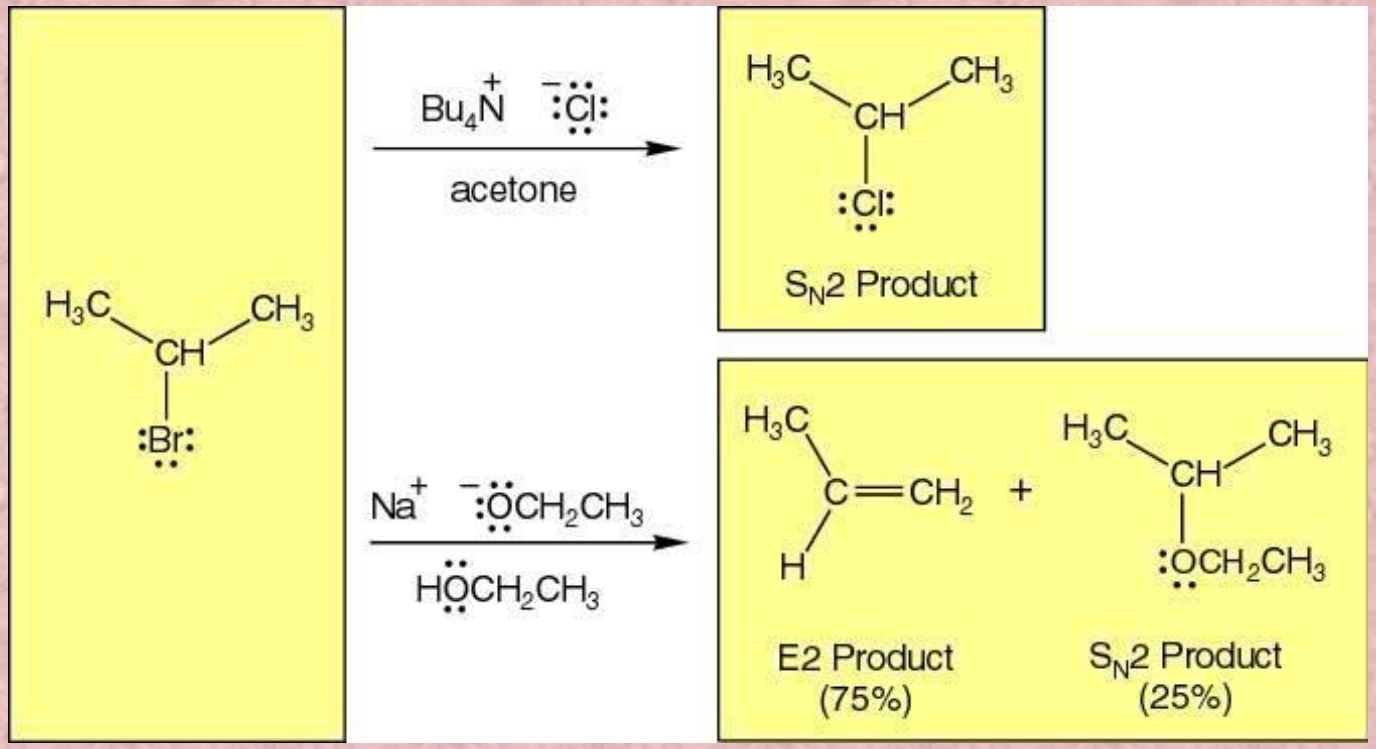


J. E2 - elimination bimolecular - one step just like S_N2

1. mechanism:

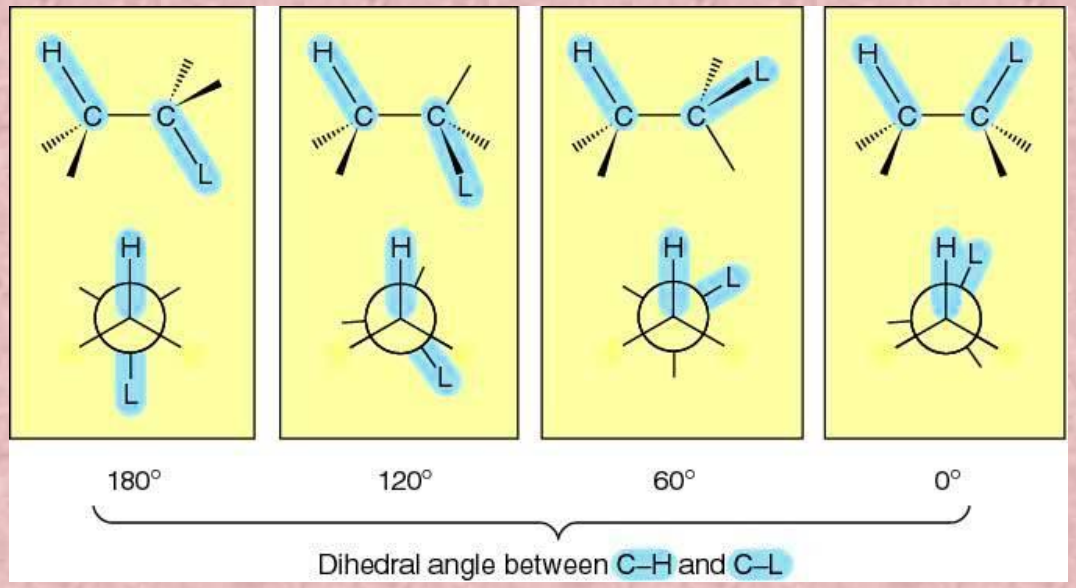


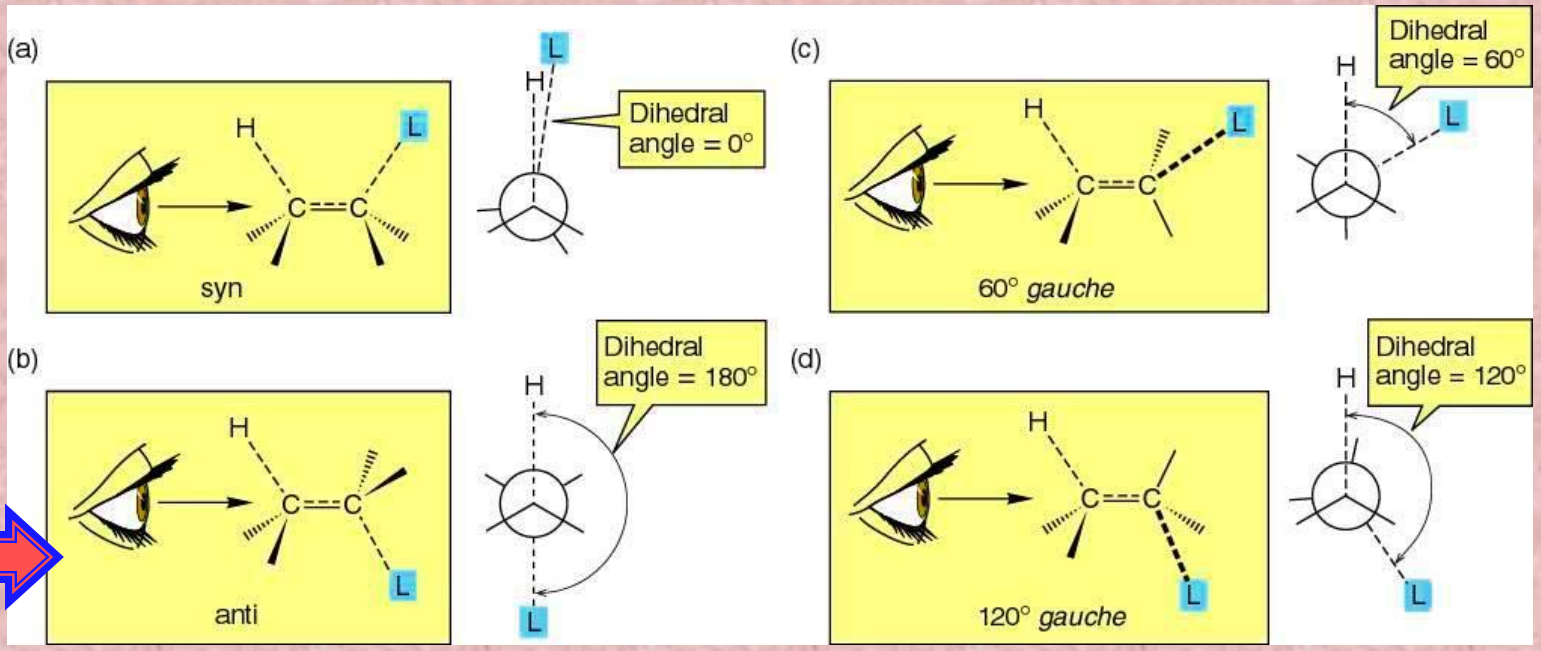
Strong bases are needed for E2 - but there is competition with S_N2

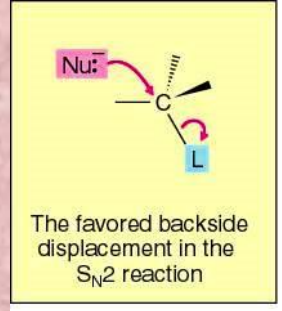


2. Stereochemistry - (there is none for E1- forms an achiral carbocation) - but for E2:

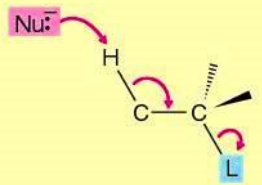
anti-peri-planar stereochemistry



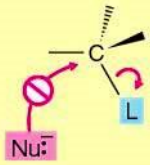




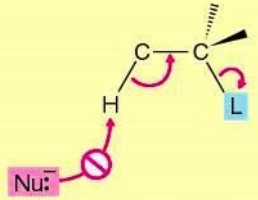
The favored backside displacement in the S_N2 reaction



The 180° E2 reaction: the electrons in the C–H bond displace the leaving group from the rear

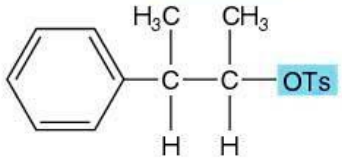


The disfavored frontside S_N2 displacement



The 0° E2 mimics the frontside S_N2 reaction: the electrons in the C–H bond displace the leaving group from the front

Ph = C_6H_5 OTs = Tosylate, an excellent leaving group (see Fig. 6.48)



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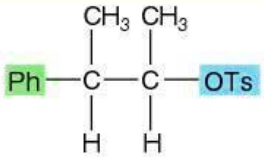
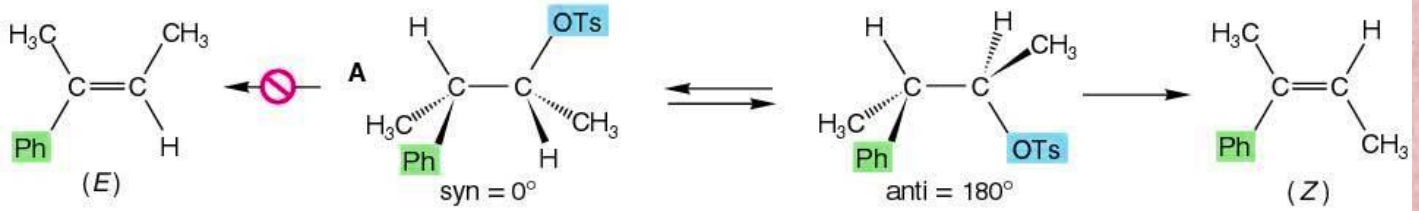
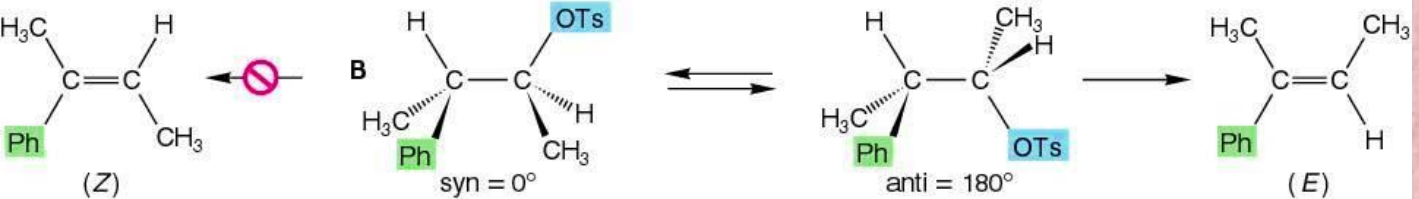
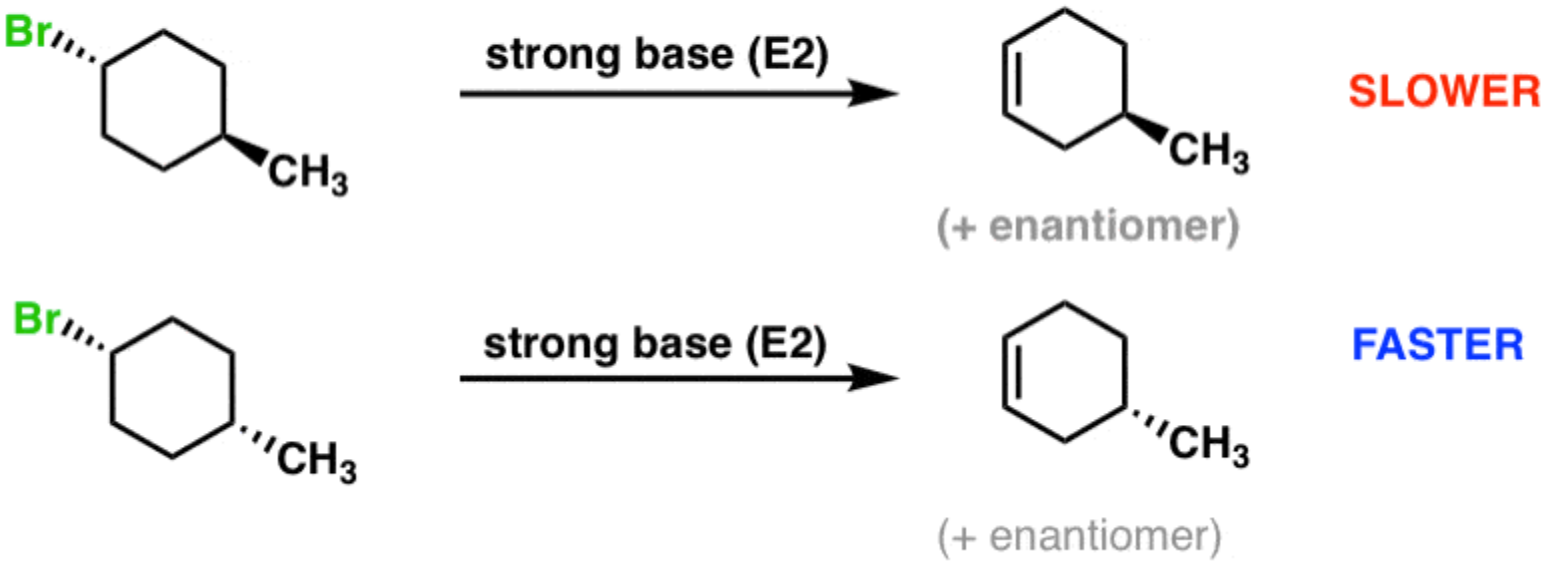


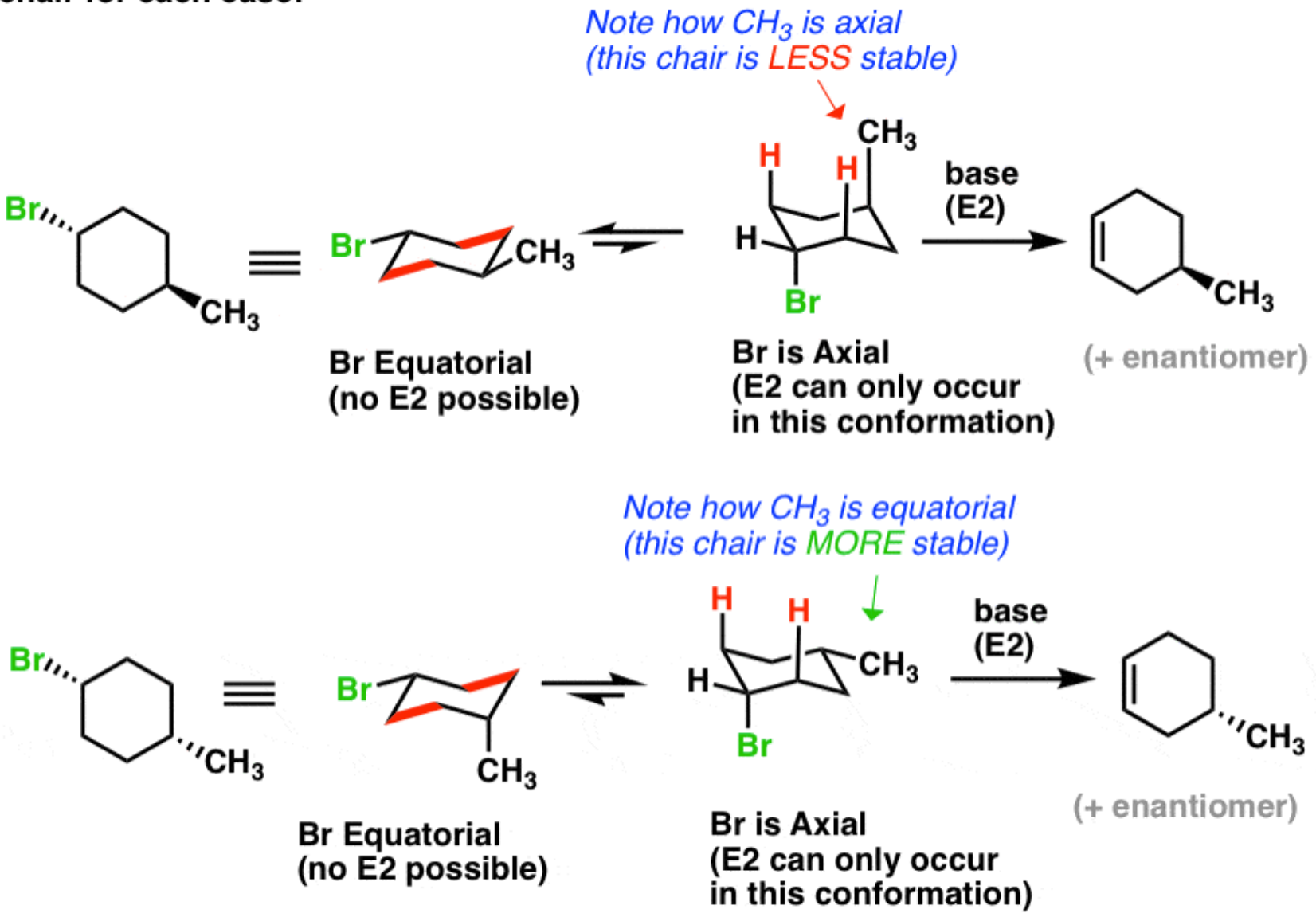




Application: Explain the difference in rate in these two cyclohexanes!



Knowing that the elimination must occur when Br is axial, draw the corresponding chair for each case:



- The bottom reaction will occur more quickly because it goes through a **more stable** chair conformation (when Br is axial, CH_3 is equatorial)

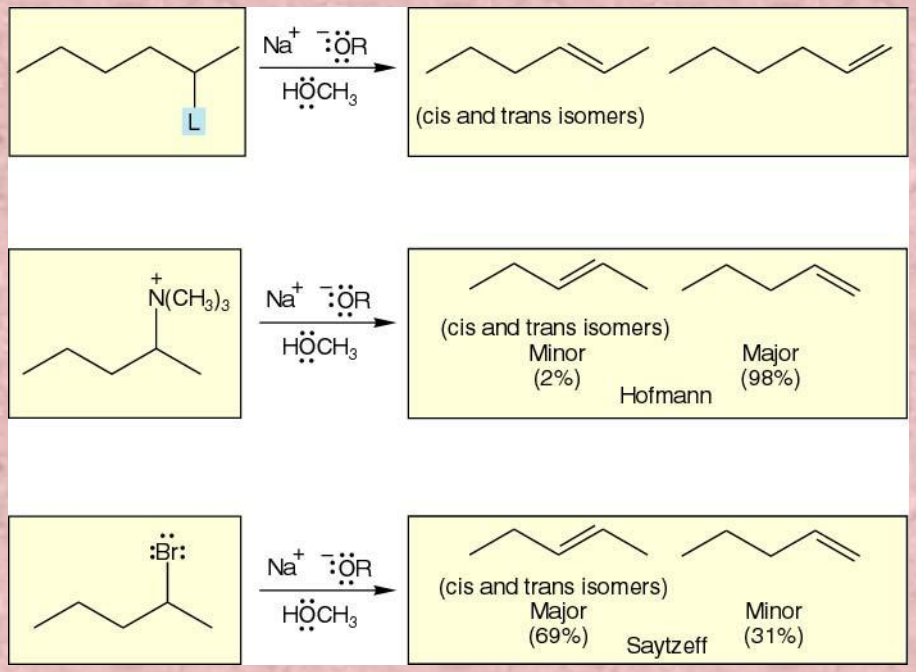
What's going on?

Each molecule will have an equilibrium between two chair forms.

In the top molecule, the left-hand conformation is favored, because the bulky methyl group* [CH_3 is actually bulkier than Br] is equatorial. So equilibrium will favor the left hand molecule.

In the bottom molecule, the rightmost conformation is favored, because the bulky methyl group is equatorial. So equilibrium will favor the right-hand molecule.

3. Orientation - mainly follows the Saytzeff rule (most substituted olefin) - HOWEVER - there is another pattern! The Hofmann orientation - the least substituted olefin is formed:

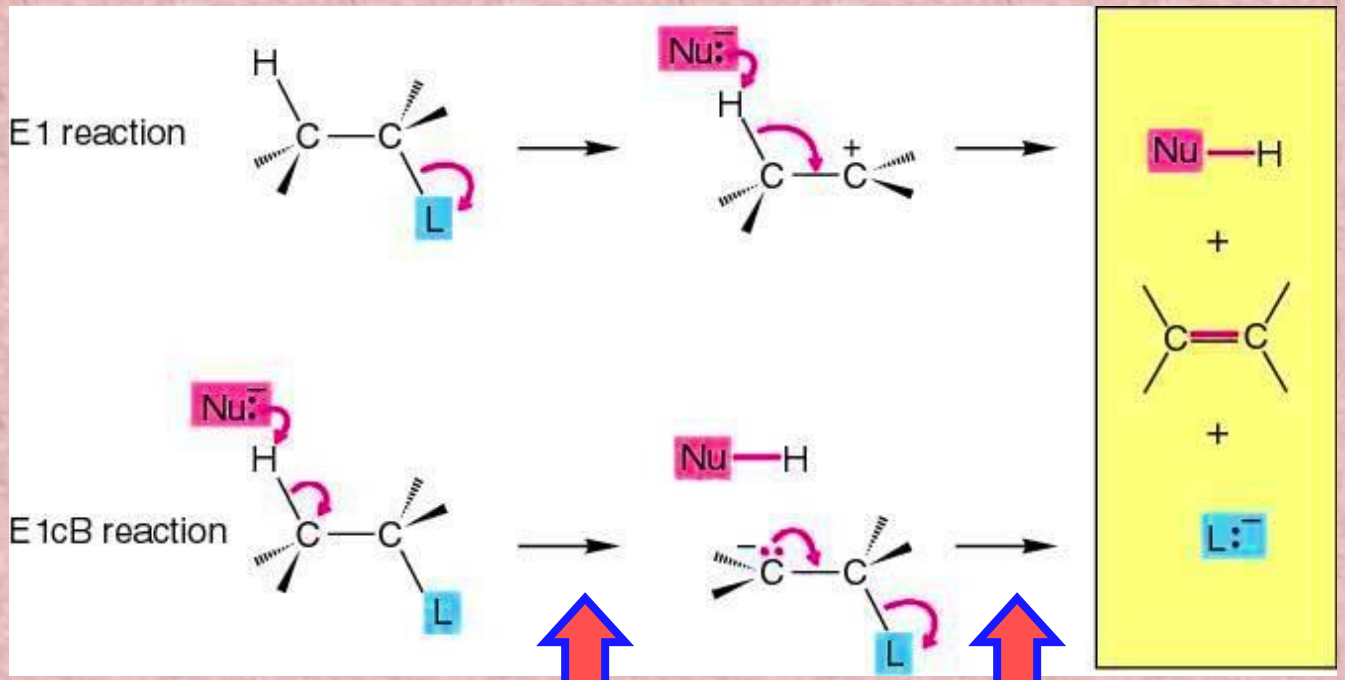


Hofmann rule

Saytzeff rule

The difference in orientation here is (obviously) due to the nature of the leaving group, L…

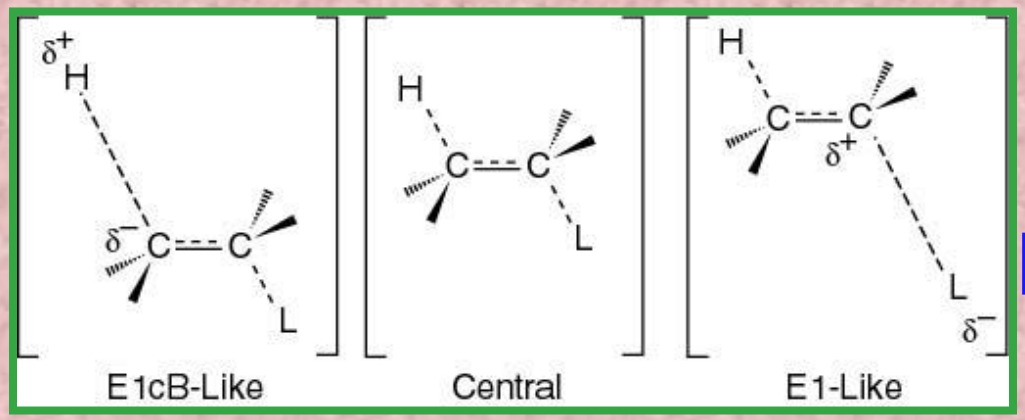
The orientational preference for the Hofmann rule is derived from a change in the nature of the E2 mechanism. Let us first look at the third mechanism - E1cB - elimination unimolecular carbon base:



In reality there is a spectrum of reaction mechanisms!!

The transition states look like -

“pure”
E1cb



“pure”
E1

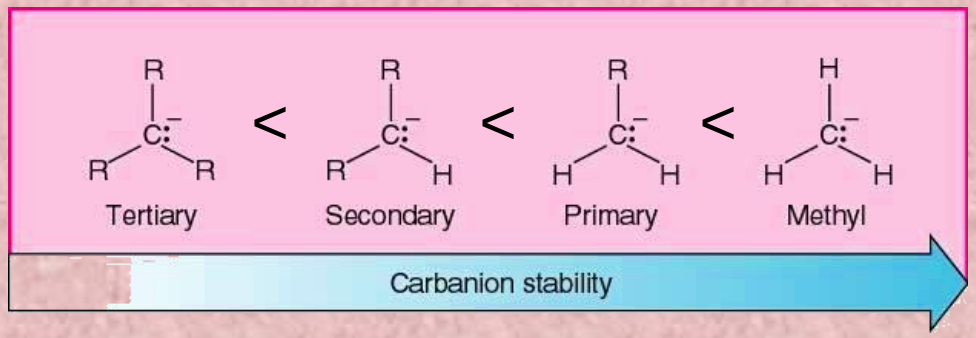
E2

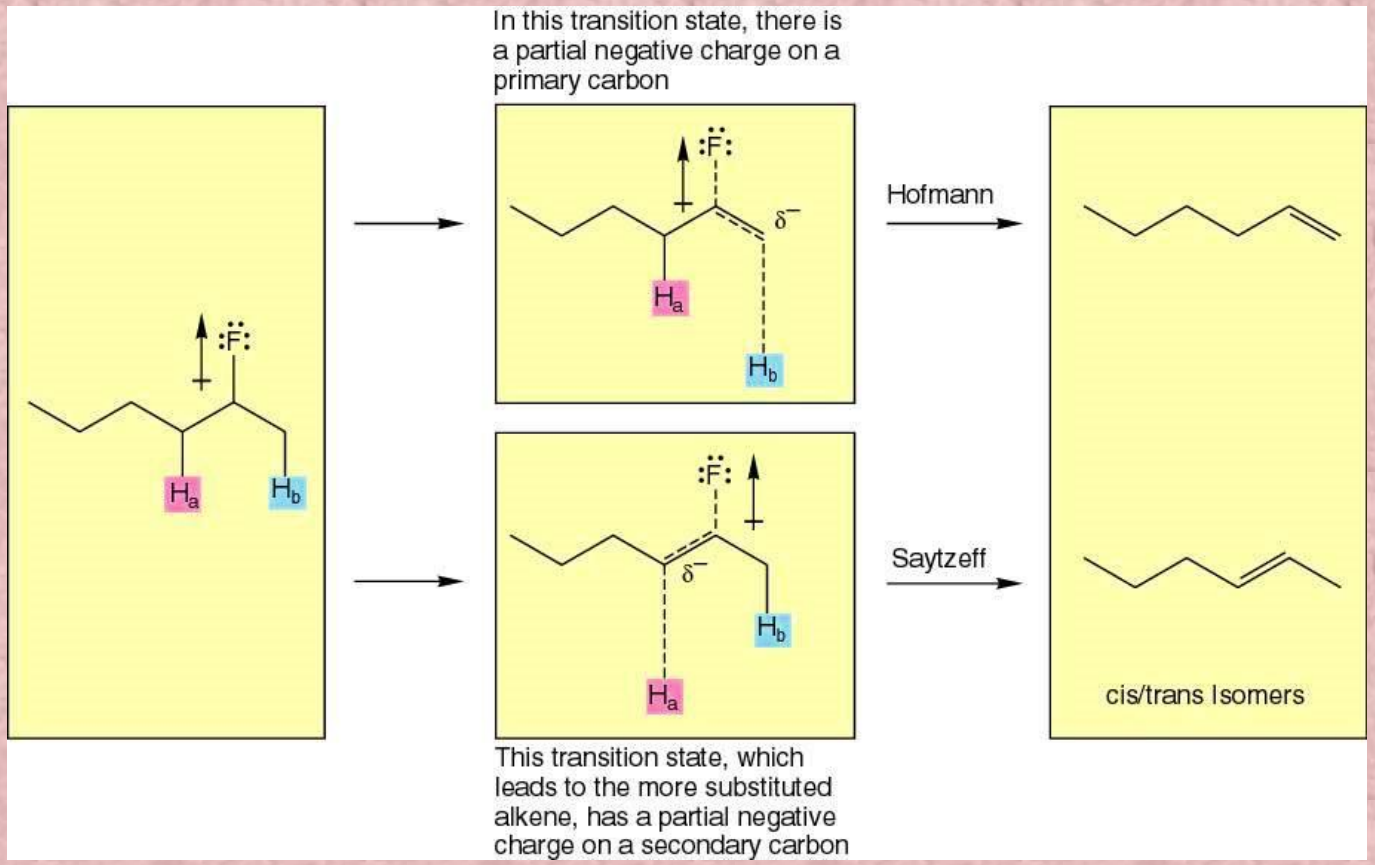
Hofmann

Saytzeff

So if L is a strongly electron withdrawing group -
e. g. -F or -$N(NMe)_3$
then a E1cB or E2 with”E1cB-like” character is favored.

NOW REMEMBER - that the stability of carbanions is:





K. Substitution versus eleimination - general patterns:

1. Strong bases - favor S_N2 or E2.
2. Weak bases - favor S_N1 or S_N2.
3. Bulky bases ($Me_3C\text{-}O^-$ etc.) favor elimination.
4. Polarizable bases (Me_3P, etc) favor substitution.
5. Primary halides - usually undergo S_N2 -
   except if we are using a very, very strong base, then E2.
6. Tertiary halides - usually undergo E2 with a strong base but a combination of S_N1/E1 with a weak base.
7. Good leaving groups (form stable bases) favor S_N1 or E1.
8. High temperatures promote elimination ($-T\Delta S$ term).

J. Summary

1. Nomenclature of R-X.
2. Preparation -
    a. allylic halogenation -NBS.
3. Nucleophilic substitution
    a. mechanisms of S_N1 and S_N2
    b. rate laws and stereochemistry
    c. variation of nucleophile, structure of R group, solvent and leaving group, L on reaction rates
    d. rearrangements in carbocations
4. Elimination reactions
    a. mechanisms of E1, E2 and E1cB
    b. stereochemistry and rate laws
    c. orientation - Saytzeff versus Hofmann
    d. effect of base, leaving group and alkyl group
5. Factors favoring substitution versus elimination