

CH 209 – Basic Organic Chemistry

Reaction mechanisms: Substitution reactions (S_N1 and S_N2)



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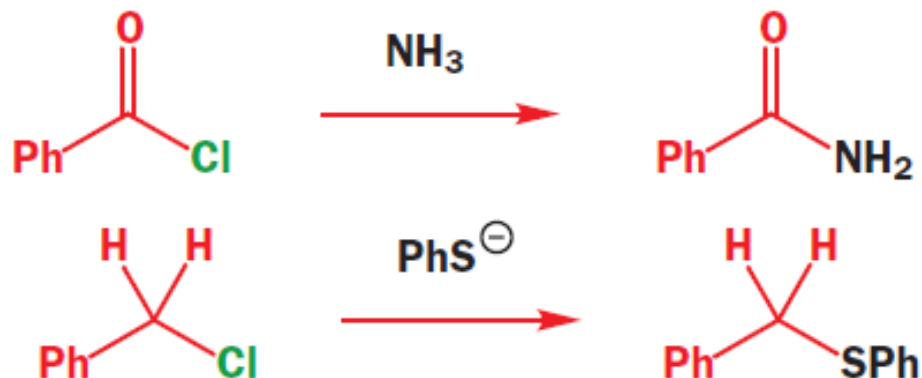


Types of organic reactions

- **Substitution reactions** – replace one group with another, S_N2 , S_N1 etc.
- **Elimination reactions** – take something off, $E2$, $E1$ etc. Usually, *two* groups come off and an alkene is formed!
- **Addition reactions** – add something on! Usually you add two groups to an alkene
- **Rearrangement reactions** – The carbon skeleton of a molecule is rearranged to give a structural isomer of the original molecule
- **Pericyclic reactions** – the transition state of the molecule has a cyclic geometry, the reaction progresses in a concerted fashion, and the bond orbitals involved in the reaction overlap in a continuous cycle at the transition state.
- **Oxidation reactions**
- **Reduction reactions**

Substitution reactions

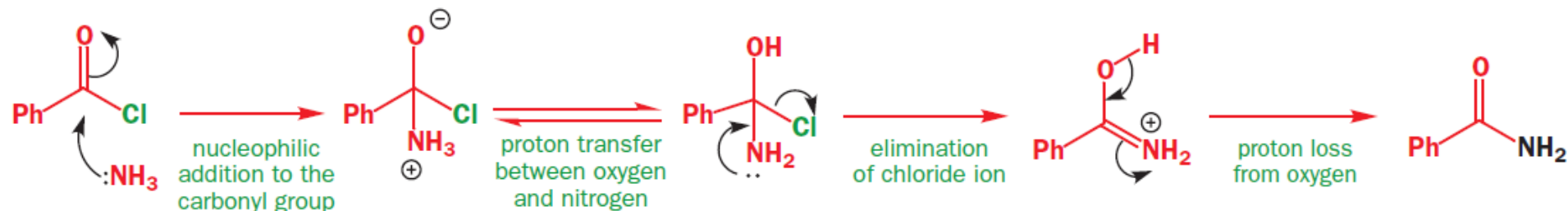
- Substitution is the replacement of one group by another



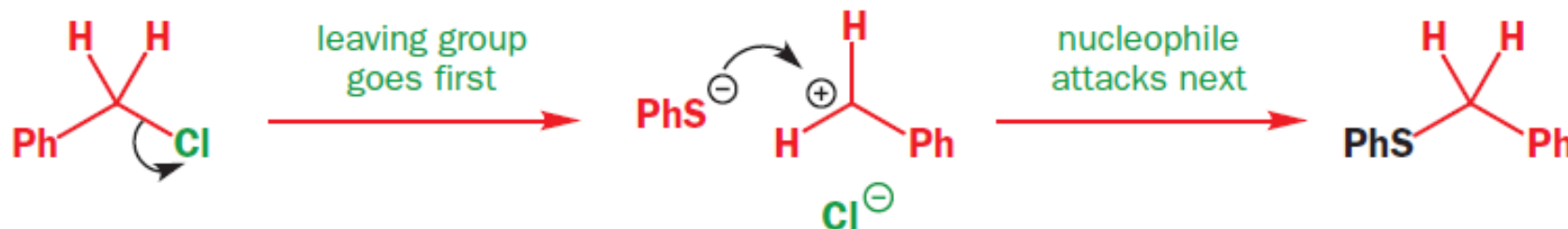
- ❖ Label the nucleophile and electrophile in this substitution reaction!
- ❖ Write the plausible mechanisms!

Substitution reactions

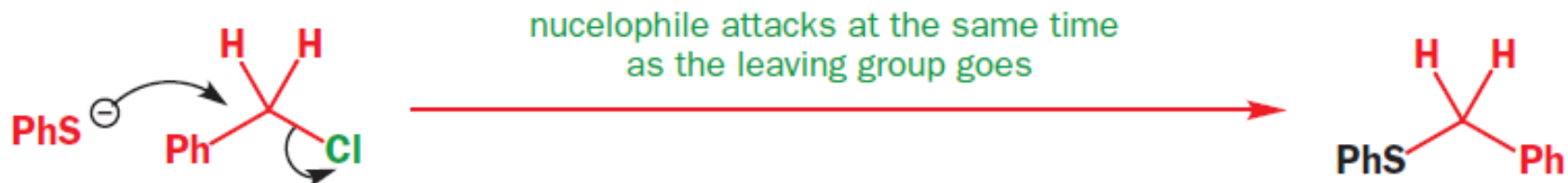
mechanism of nucleophilic substitution at the carbonyl group



the $\text{S}_{\text{N}}1$ mechanism



the $\text{S}_{\text{N}}2$ mechanism

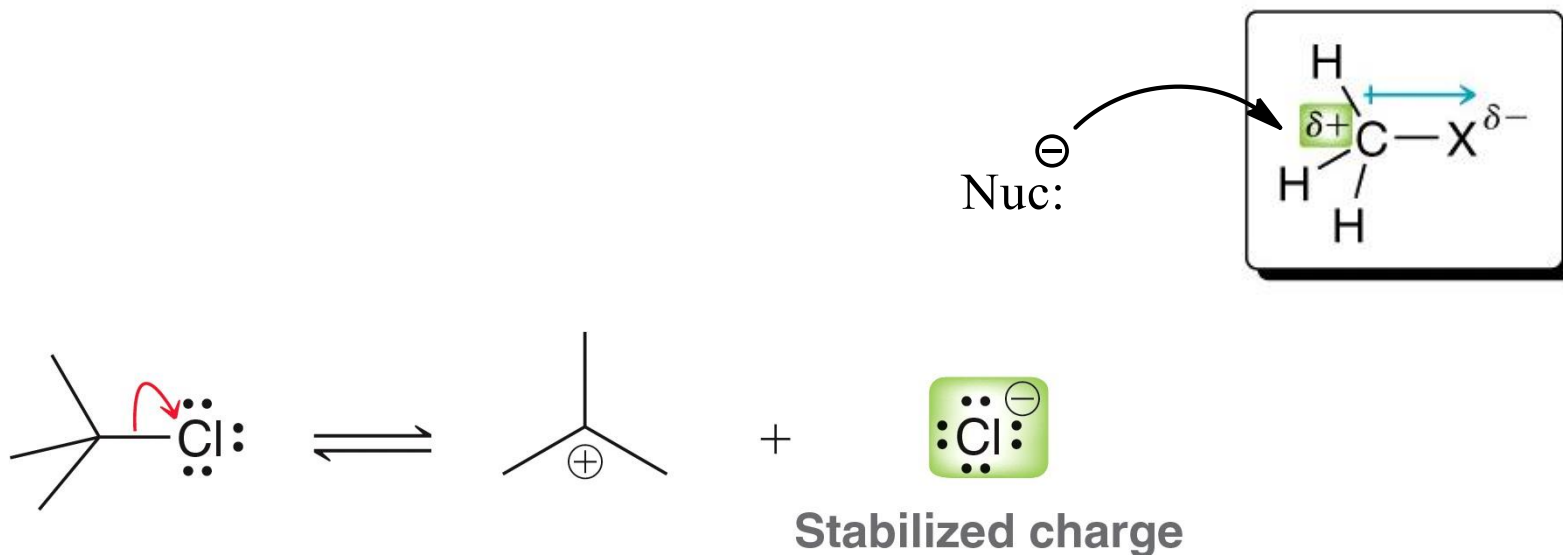


❖ Mechanisms of substitution reactions at saturated carbon and unsaturated carbon are very different!!

Substitution reactions

To encourage substitution, a good leaving group must fulfill two criteria:

1. The electronegative leaving group creates a partial charge on the site of attack to attract the negative charge of the nucleophile
2. The leaving group must be able to stabilize the electrons it leaves with!

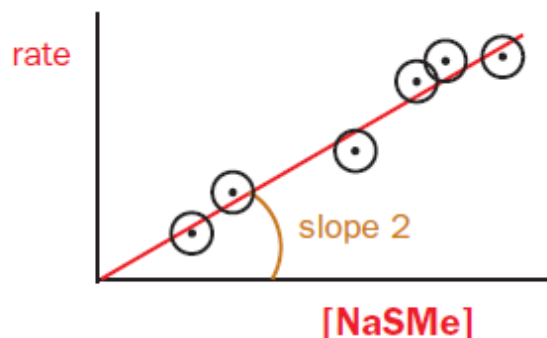
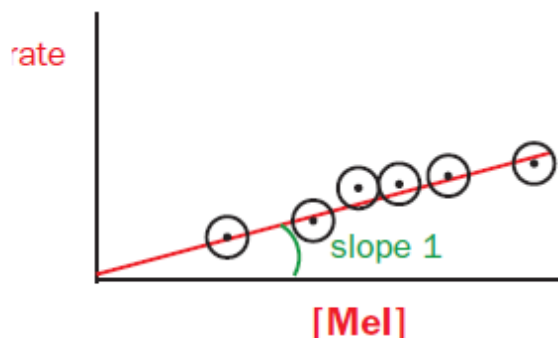


Substitution mechanisms

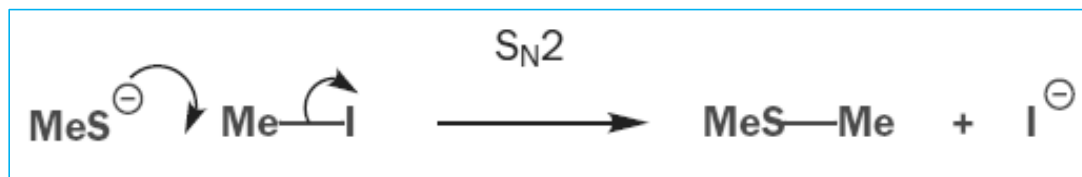
1. Nucleophilic attack first then loss of leaving group.
2. Loss of leaving group first then nucleophilic attack
3. Both happen simultaneously

The S_N2 reaction

Kinetics for S_N2 mechanisms for nucleophilic substitution



$$\text{Rate} = k_2[\text{MeSNa}][\text{MeI}]$$



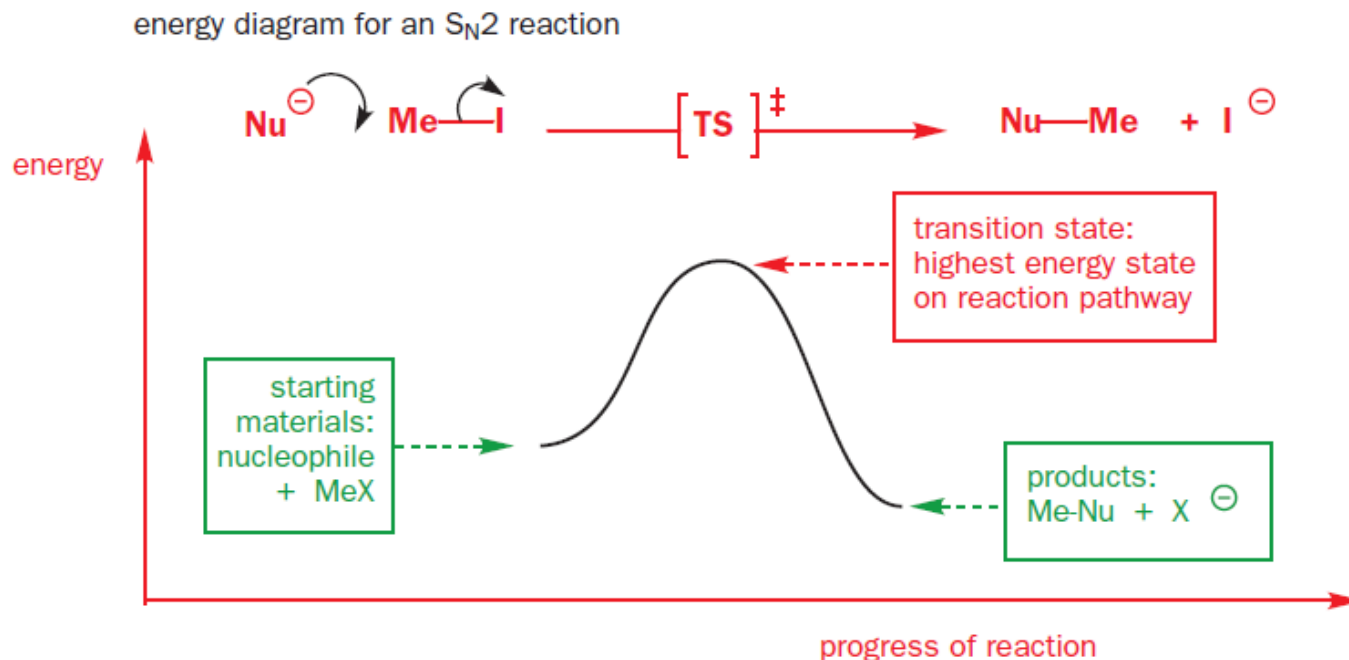
❖ Substitution, Nucleophilic, 2nd Order or S_N2 for short!!

The S_N2 reaction

$$\text{rate} = k_2[\text{nucleophile}][\text{MeX}]$$

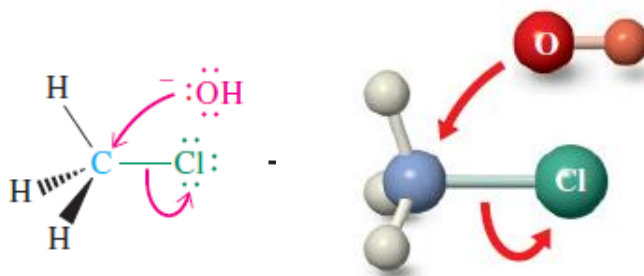
- Rate of an S_N2 reaction is proportional both to the concentration of the nucleophile and to the concentration of the alkyl halide (MeX)

Reaction coordinate diagram

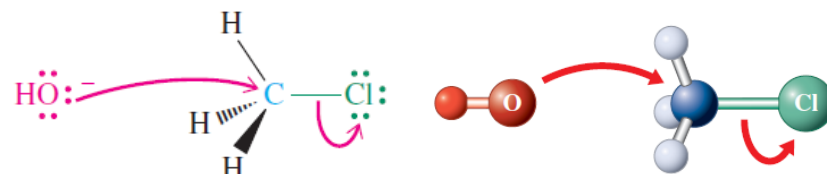


The S_N2 reaction – Concerted mechanism

- Bimolecular nucleophilic substitution is a one-step transformation: The nucleophile attacks the haloalkane, with simultaneous expulsion of the leaving group.
- Bond making takes place *at the same time* as bond breaking.
- Because the two events occur “in concert,” we call this process a **concerted** reaction.
- The nucleophile could approach the substrate from the same side as the leaving group, one group exchanging for the other - **frontside displacement**
- The second possibility is a **backside displacement**, in which the nucleophile approaches carbon from the side opposite the leaving group



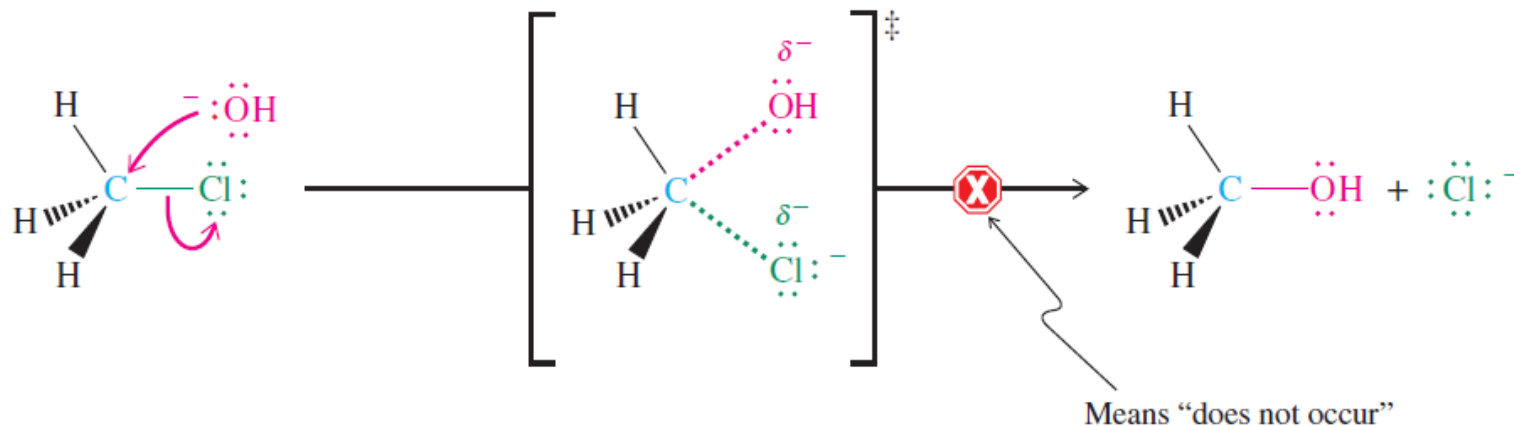
Frontside displacement



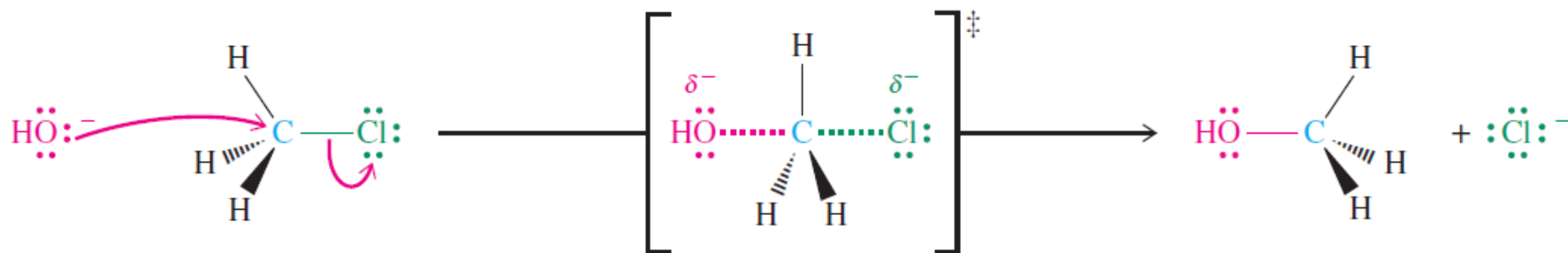
Backside displacement

The S_N2 reaction – Concerted mechanism

Front-side displacement

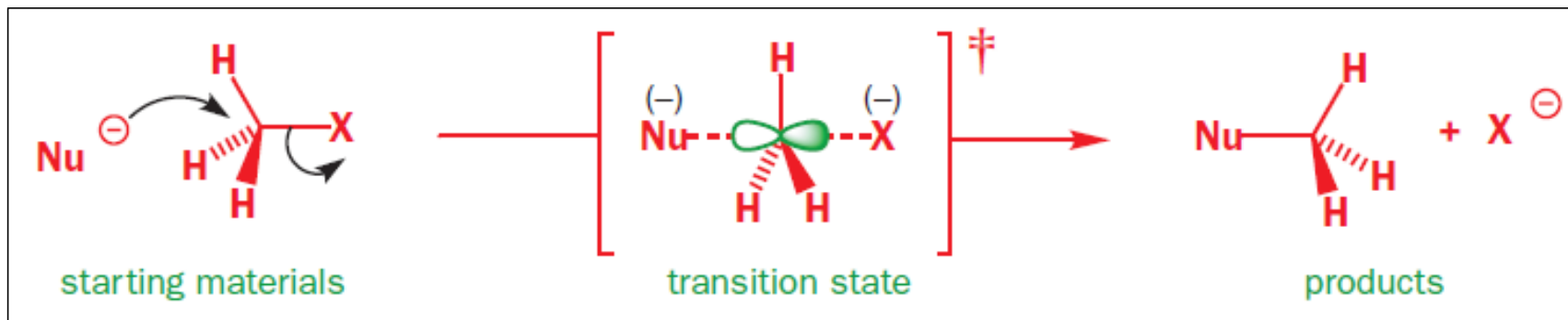


Backside displacement



- The two methanol pictures are related as object and mirror image.
- The two are superimposable and therefore indistinguishable properties of an achiral molecule

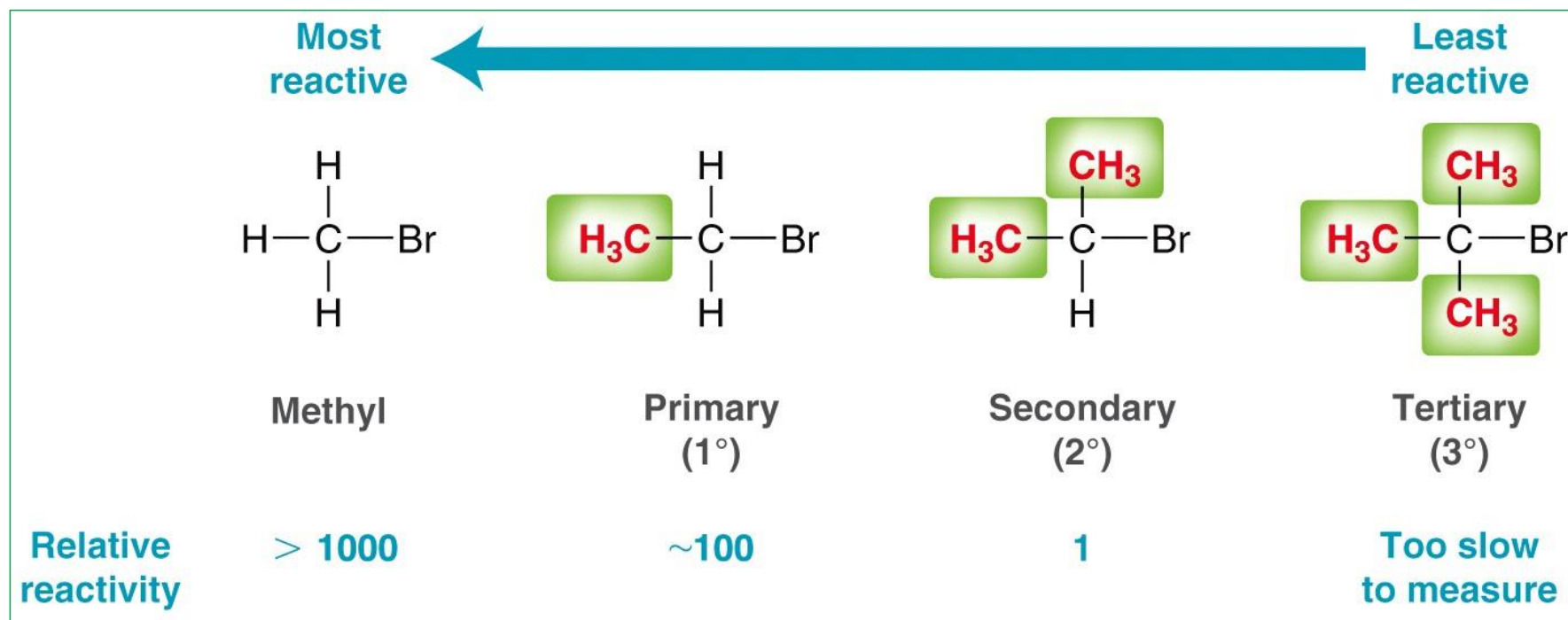
The S_N2 reaction



- The transition state for an S_N2 reaction has a more or less planar carbon atom at the centre with the nucleophile and the leaving group arranged at 180° to each other.
- The nucleophile attacks the carbon atom on the opposite side from the leaving group
- The carbon atom turns inside out as the reaction goes along, just like an umbrella in a high wind
- If the carbon atom under attack is a stereogenic centre the result will be inversion of configuration.

The S_N2 reaction - Kinetics

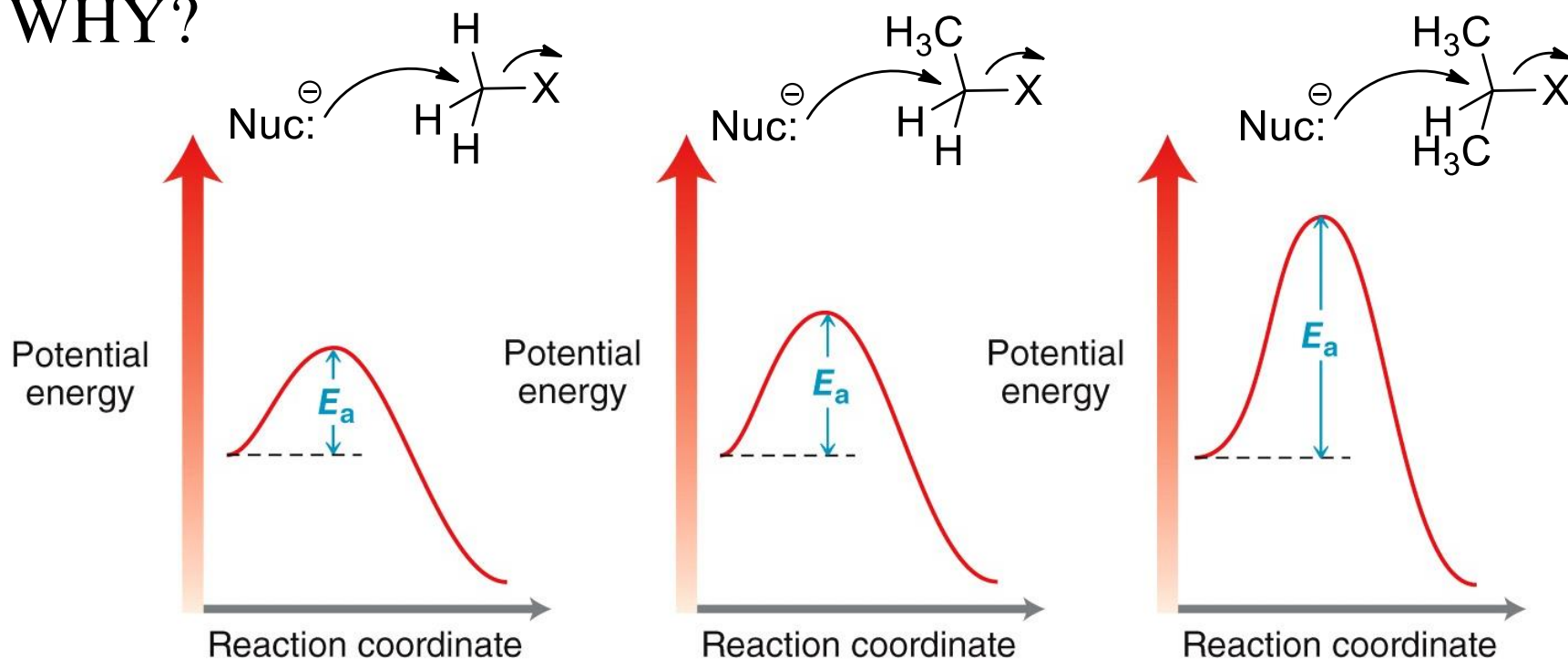
- Less sterically hindered electrophiles react more readily under S_N2 conditions.



- To explain this trend, we must examine the reaction coordinate diagram

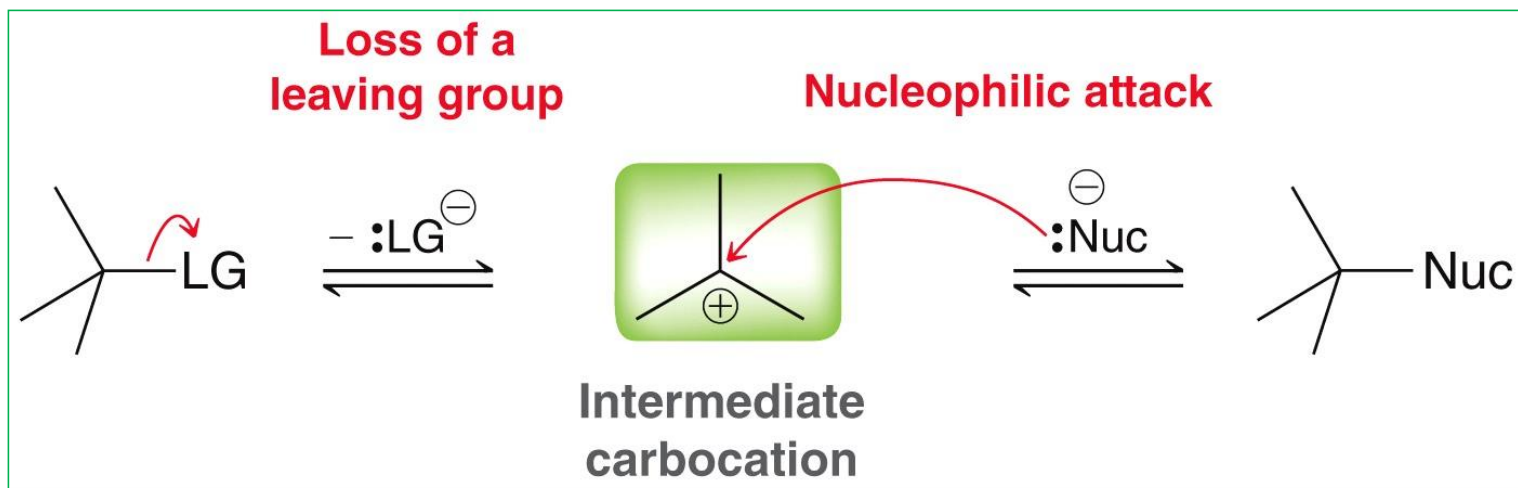
The S_N2 reaction - Kinetics

- Which reaction will have the fastest rate of reaction?
- WHY?



- 3° substrates react too slowly to measure.

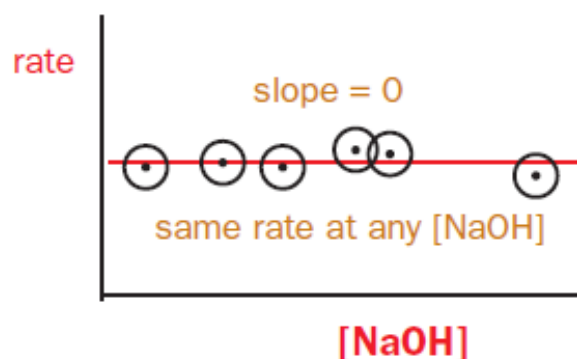
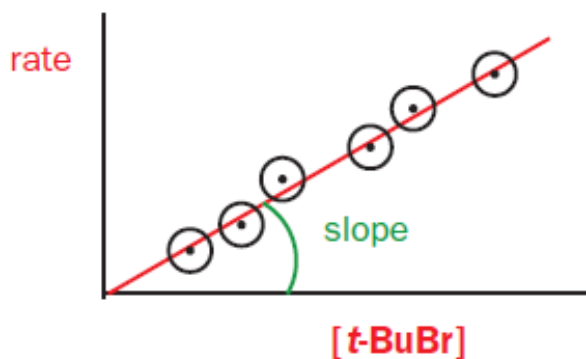
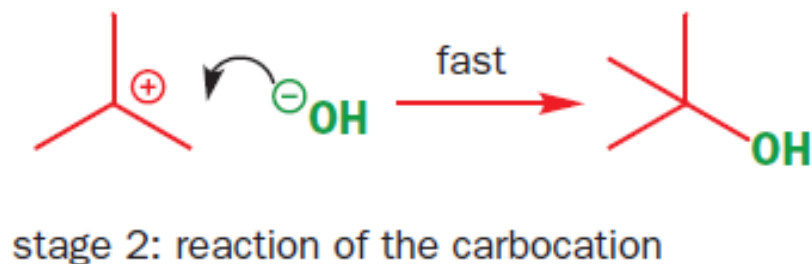
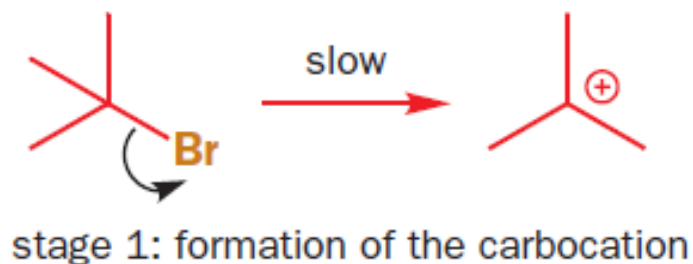
The S_N1 reactions – Two step mechanism



- Loss of leaving group first
- Forms an intermediate carbocation
- Then, nucleophile attacks

The S_N1 reactions - Kinetics

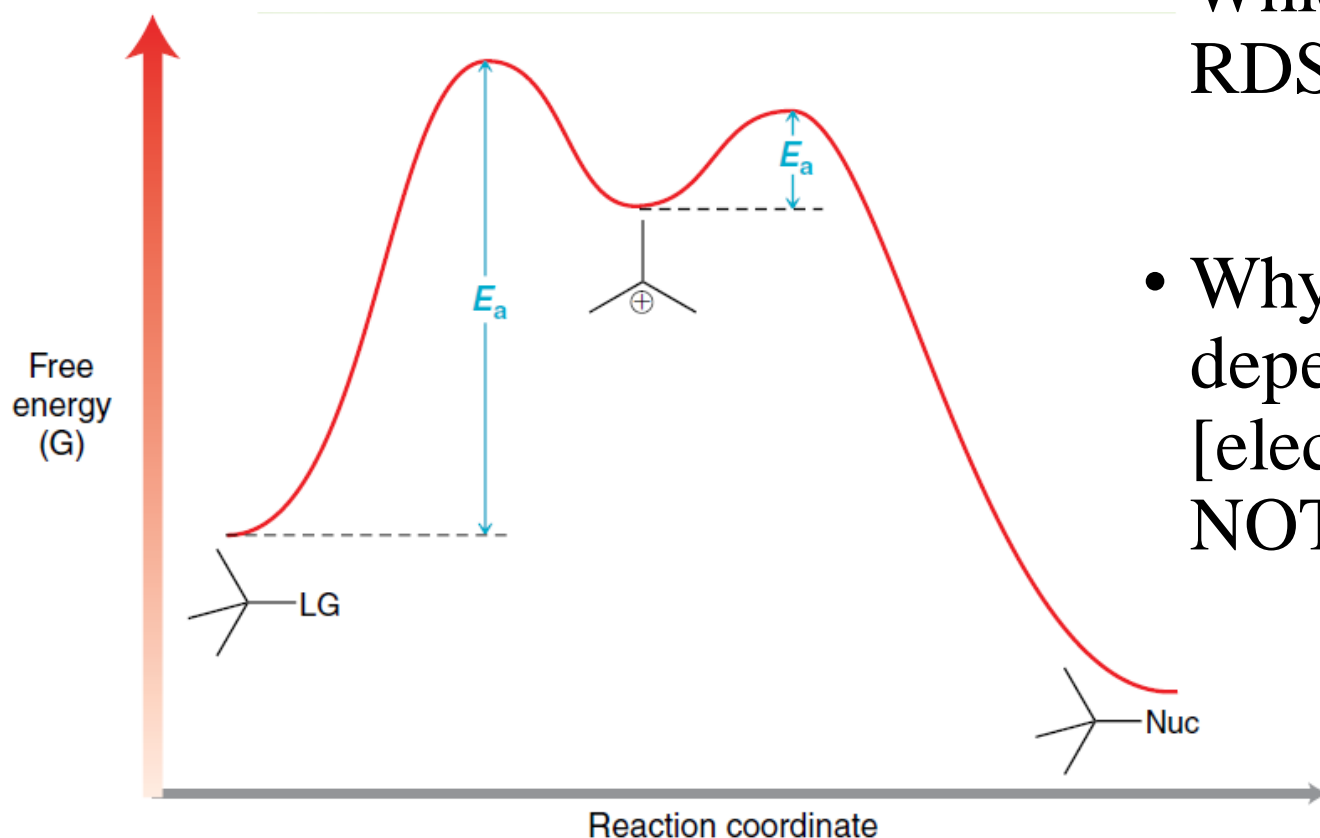
Kinetics for S_N1 mechanisms for nucleophilic substitution



$$\text{Rate} = k_1[\text{t-BuBr}]$$

❖ Substitution, Nucleophilic, 1st Order or S_N1 for short!!

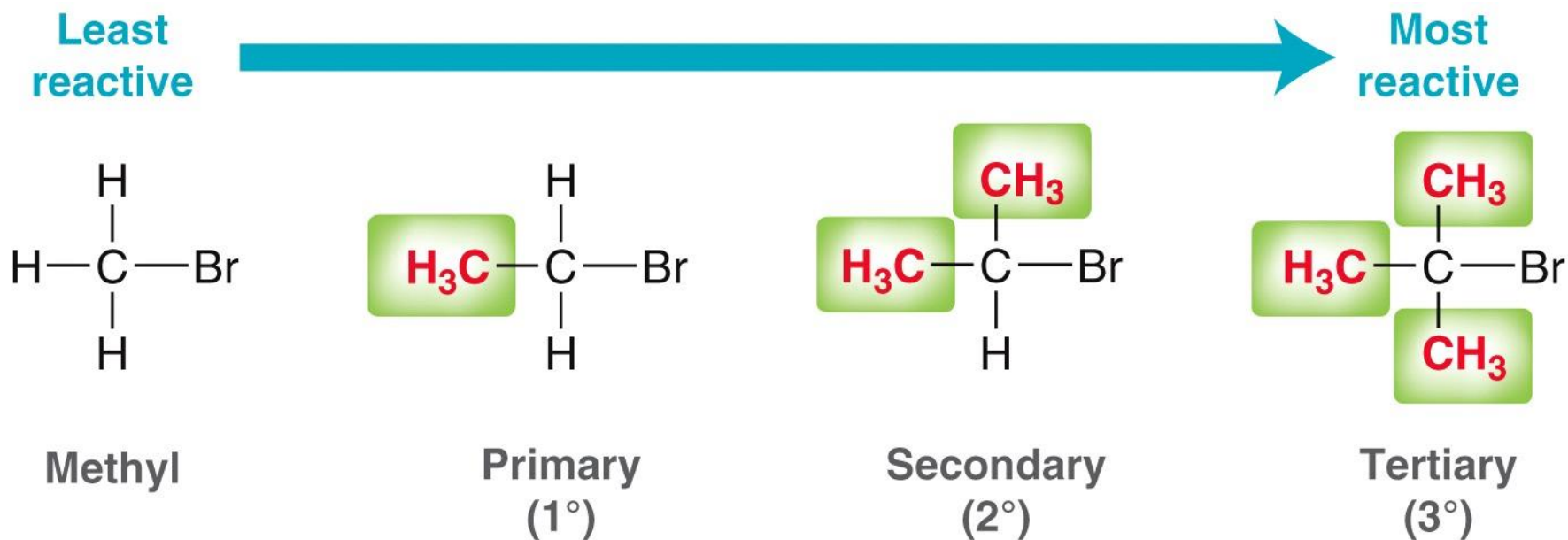
The S_N1 reactions - Kinetics



- Which step is the RDS and WHY?
- Why does the rate depend only on [electrophile] and NOT [nucleophile]?

The S_N1 reactions - Kinetics

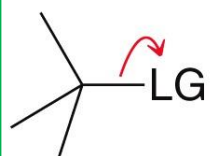
- The structure-rate relationship for S_N1 is the opposite of what it was for S_N2.



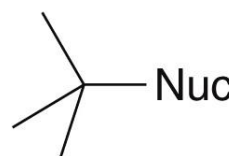
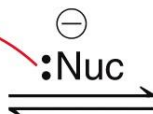
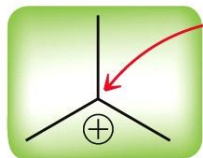
- To explain this trend, we must examine the mechanism and the reaction coordinate diagram

The S_N1 reactions - Kinetics

Loss of a leaving group

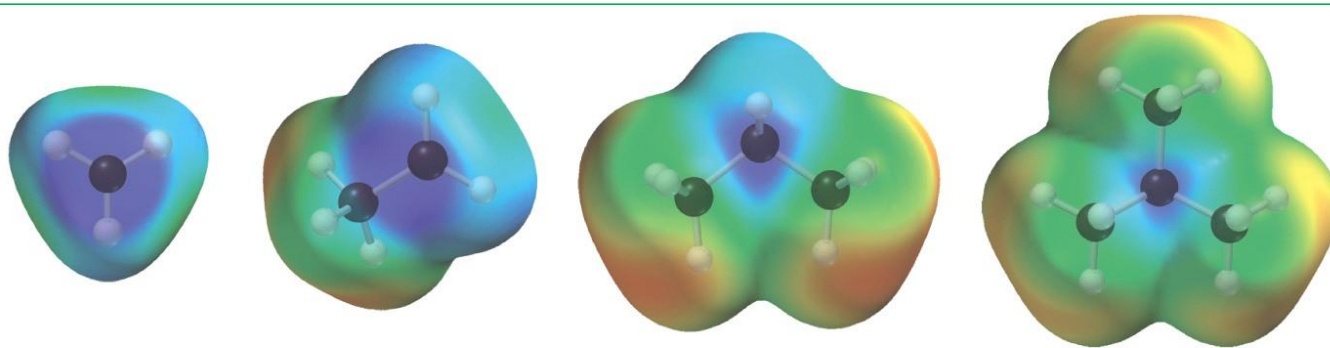


Nucleophilic attack



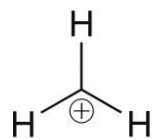
Intermediate carbocation

If the carbocation is more substituted with carbon groups, it should be more stable

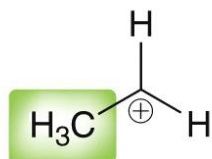


Least stable

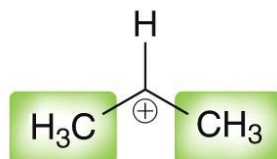
Most stable



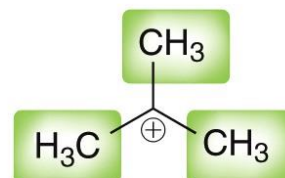
Methyl



Primary
(1°)



Secondary
(2°)

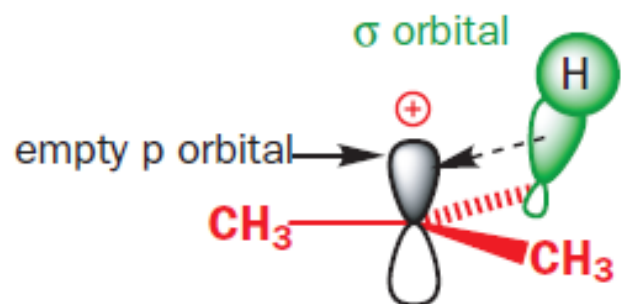


Tertiary
(3°)

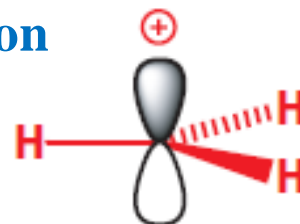
HOW do carbon groups stabilize a carbocation?

Structure and stability of carbocations

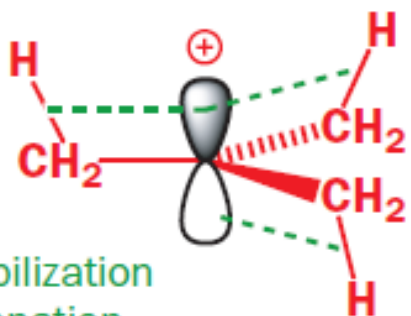
- Extra stabilization comes to the planar structure from weak donation of σ bond electrons into the empty p orbital of the cation



Hyperconjugation



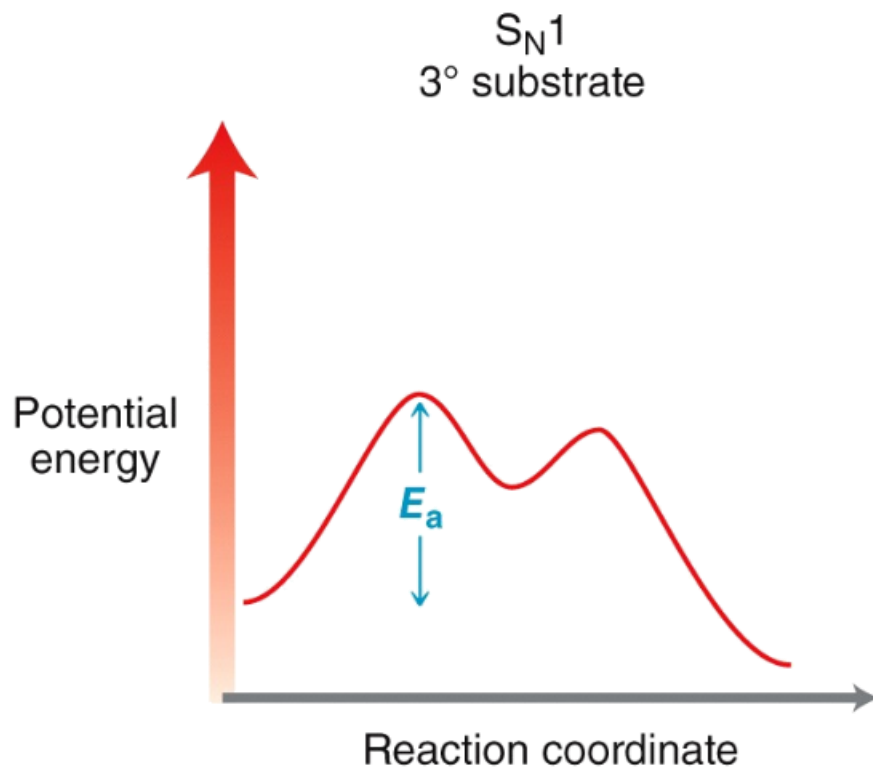
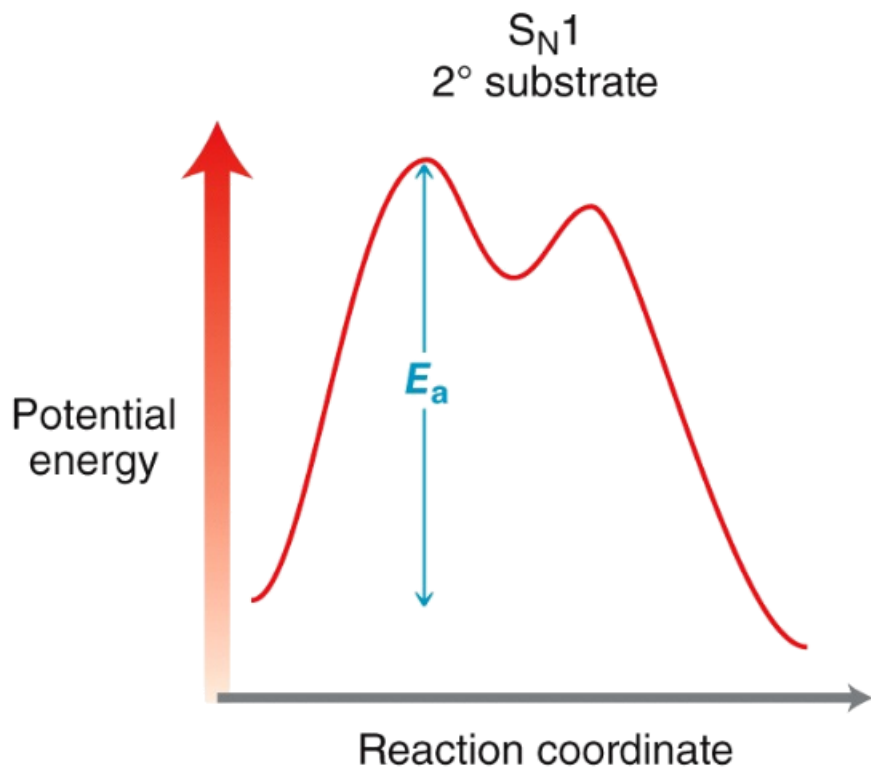
no stabilization: no electrons to donate into empty p orbital
note: The C-H bonds are at 90° to the empty p orbital and cannot interact with it



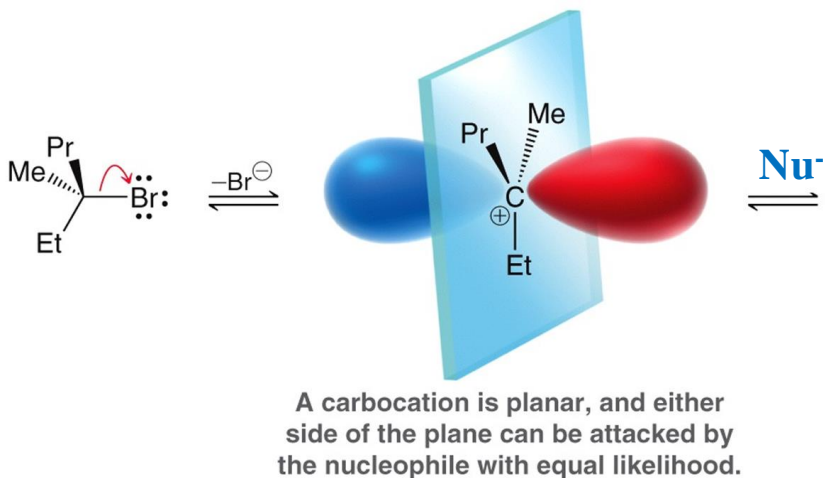
extra stabilization from σ donation into empty p orbital of planar carbocation

The S_N1 reactions - Kinetics

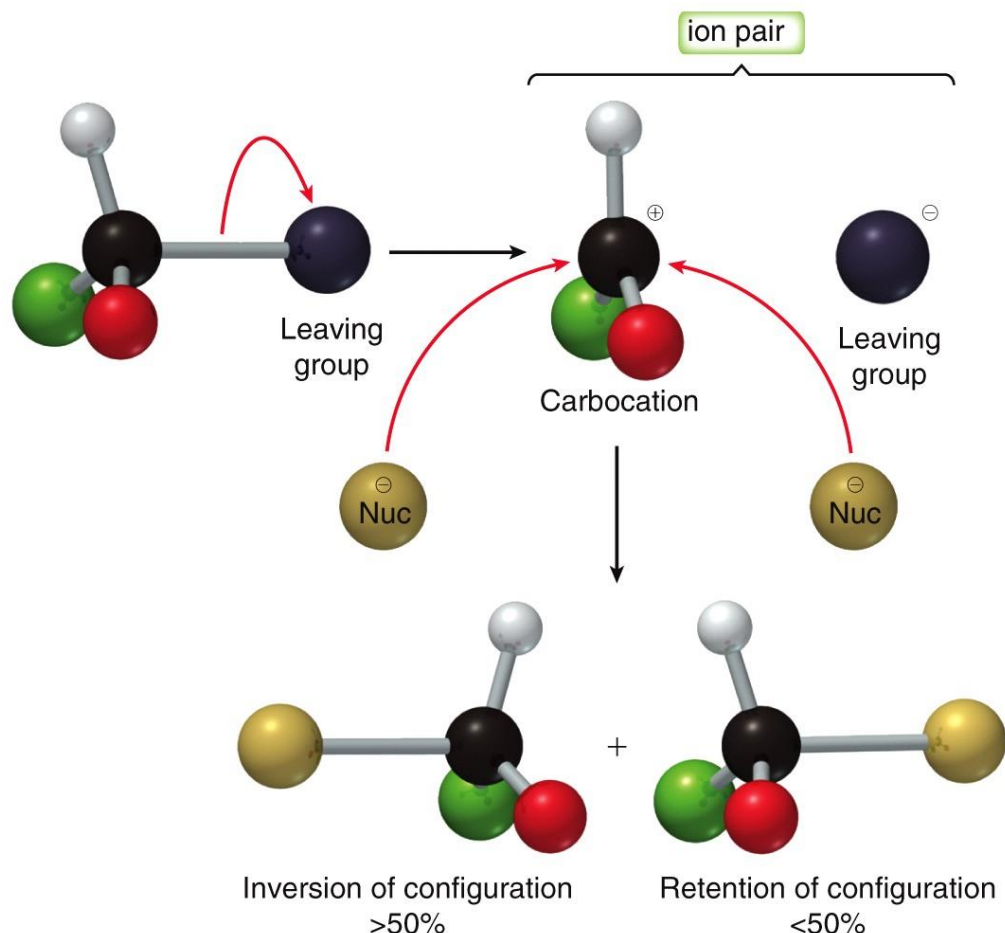
- To explain why the 3° substrate will have a faster rate, draw the relevant transition states and intermediates.
- Primary substrates react too slowly to measure.



The S_N1 stereochemistry

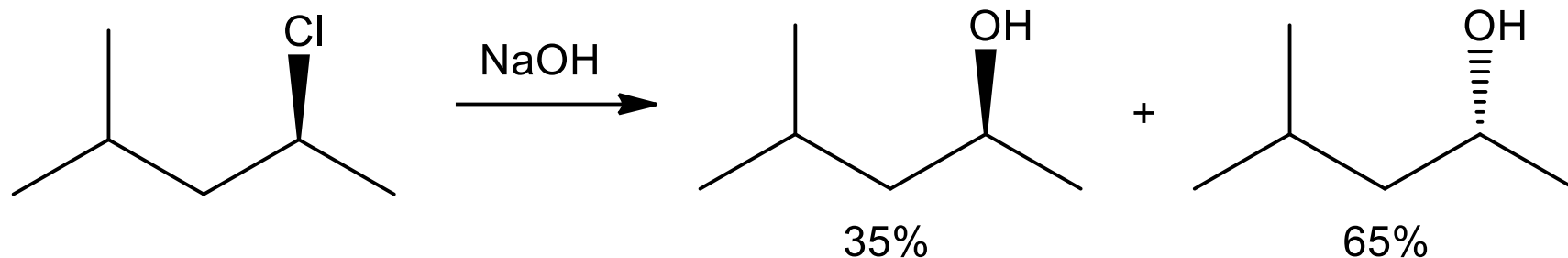


- The formation of ion pairs can cause inversion to occur slightly more often than retention



The S_N stereochemistry

- Consider the following reaction



- What accounts for the 35% and 65% product ratio?
- Is this reaction, S_N1 or S_N2?

S_N1 vs. S_N2

- There are four main factors that determine whether a substitution reaction is more likely to occur by S_N1 or S_N2
- Lets examine them in order of importance
 1. The substrate (both sterics and the stability of the carbocation)
 2. The quality of the leaving group
 3. The strength of the nucleophile
 4. The solvent

Structure and stability of carbocations

● Table 17.9 Stable carbocations as intermediates in S_N1 reactions

Type of cation

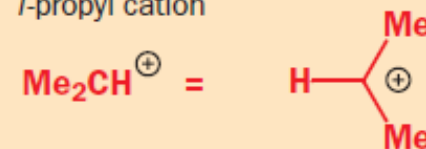
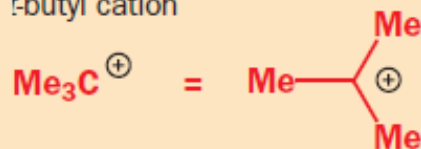
Example 1

Example 2

simple alkyl

tertiary (good)
t-butyl cation

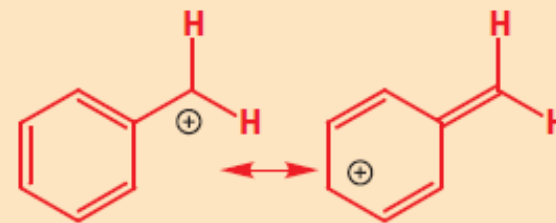
secondary (not so good)
i-propyl cation



conjugated

allylic

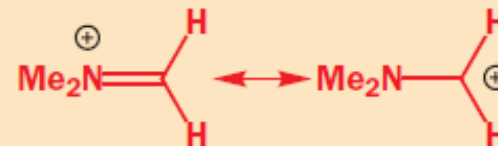
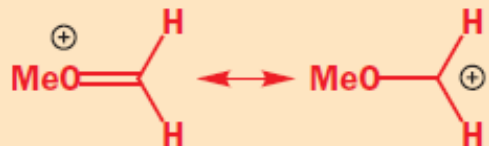
benzylic



heteroatom-stabilized

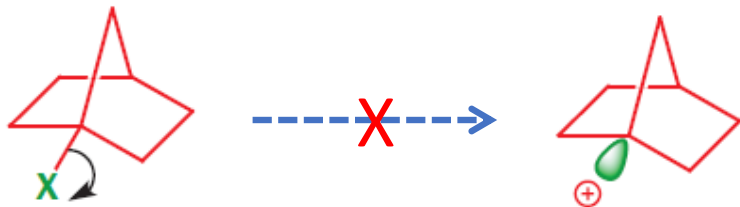
oxygen-stabilized(oxonium ions)

nitrogen-stabilized

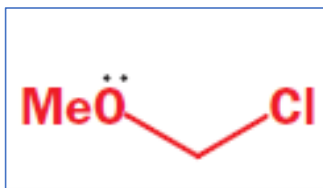


Structure and stability of carbocations

- If a tertiary cation cannot become planar, it is not formed



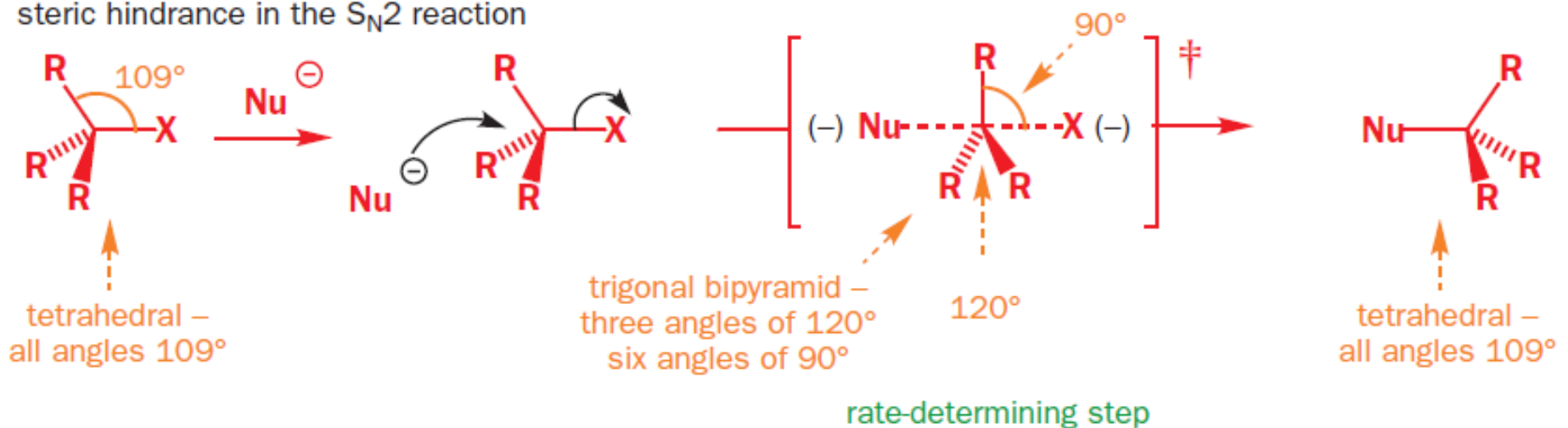
The resultant carbocation cannot be planar, hence, no S_N1 reaction takes place



Methoxymethyl chloride: Can this undergo S_N1 type of reaction?

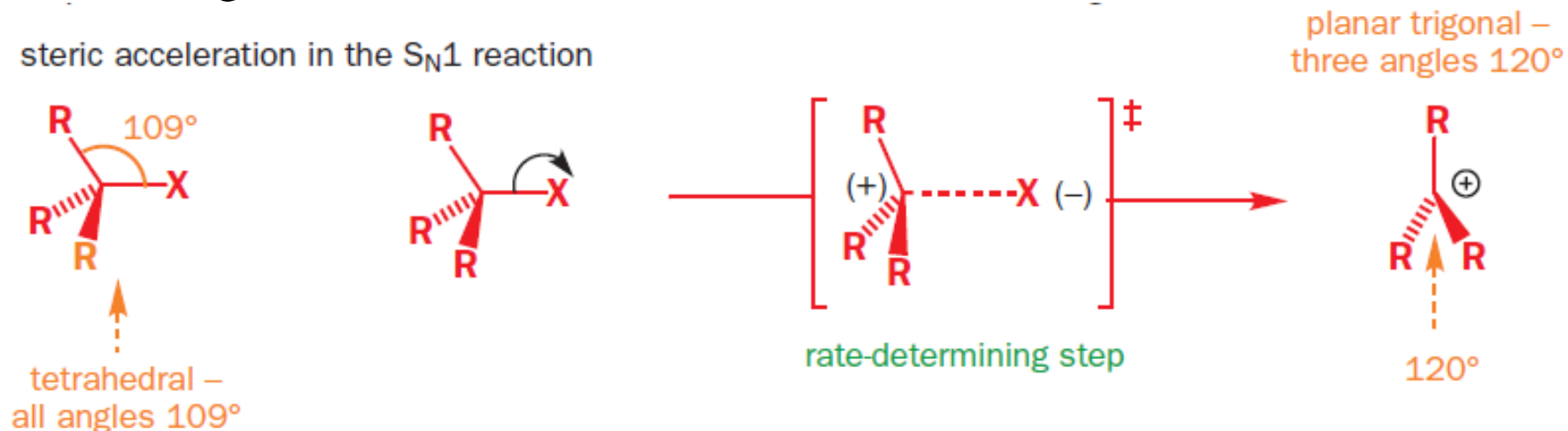
Steric hindrance in nucleophilic substitution

steric hindrance in the S_N2 reaction



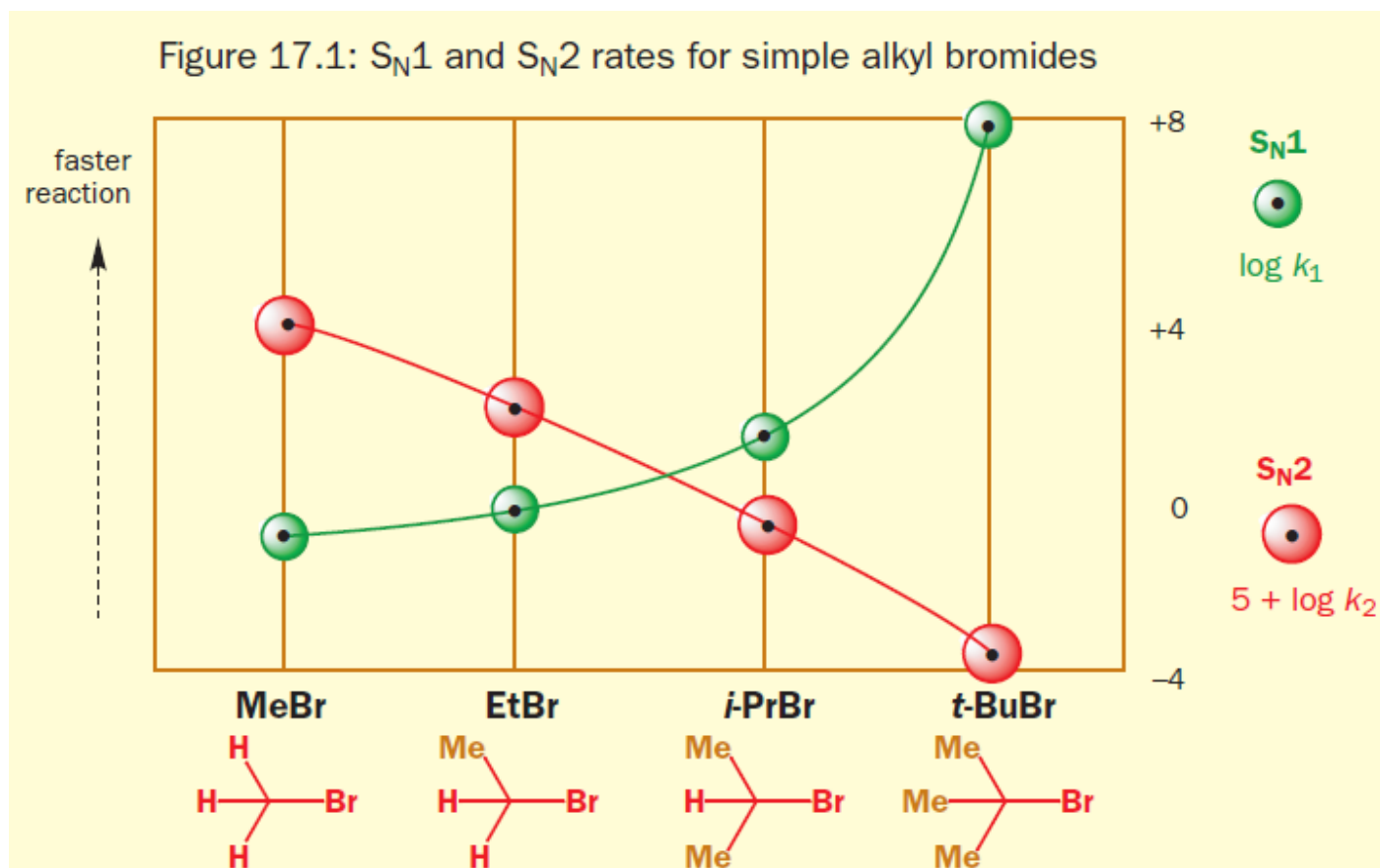
- Three angles of 120° and six angles of 90°, a significant increase in crowding.

steric acceleration in the S_N1 reaction



Steric hindrance in nucleophilic substitution

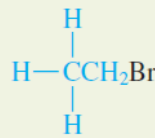
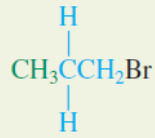
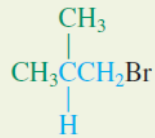
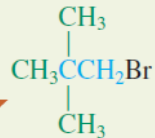
- the angles are increasing towards 120° and all interactions with the leaving group are diminishing as it moves away
- There is steric *acceleration* in the S_N1 reaction rather than steric *hindrance*.



Predict the order of reactivity in the S_N2 reaction of



- Branching next to the reacting carbon also retards S_N2 substitution

Table 6-9		Relative Reactivities of Branched Bromoalkanes with Iodide
Bromoalkane		Relative rate
<div>Decreasing reactivity</div> <div>↓</div>		1
		0.8
		0.03
		1.3×10^{-5}
	<div>Increasing size of R</div> <div>↓</div>	

S_N1 vs. S_N2 (The nucleophile)

- A stronger nucleophile favors S_N2 , although it may react by S_N1 if the substrate is sterically hindered and the leaving group is good.
- A weaker nucleophile favors S_N1 , although it may react by S_N2 if the substrate cannot stabilize a carbocation effectively, and the leaving group is poor.

Common nucleophiles

Strong			Weak
I^-	HS^-	HO^-	F^-
Br^-	H_2S	RO^-	H_2O
Cl^-	RSH	$N\equiv C^-$	ROH

- What factors make nucleophiles strong versus weak?
- Already discussed in the previous lectures

Factors that affect nucleophilicity

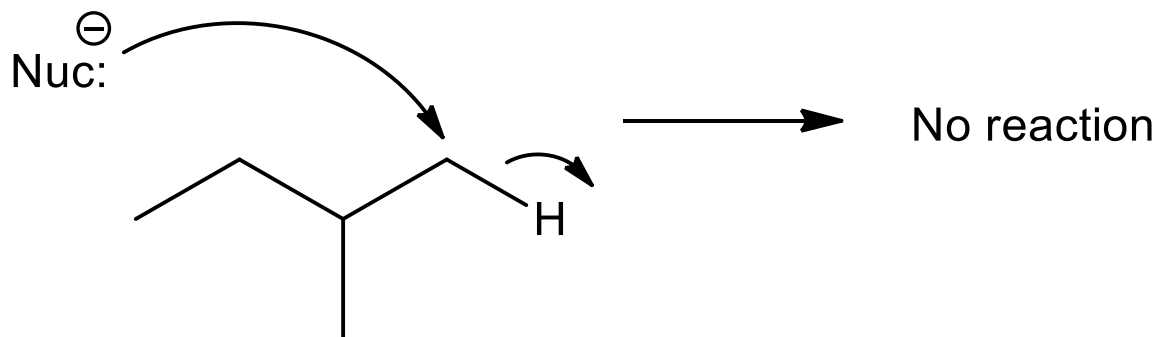
- **Charge:** The higher the electron density on a species, the more nucleophilic it is.
- **Electronegativity:** A highly electronegative atom is less willing to donate a pair of electrons
- **Size or steric hindrance:** Sterically bulky nucleophiles react more slowly
- **Solvent:** Solvation weakens the nucleophile; that is, solvation decreases nucleophilicity
- **Resonance effect on nucleophilicity:** If the electron lone pair on a heteroatom is delocalized by resonance, it is inherently less reactive

Strong nucleophile favors S_N2 . We discussed about the nucleophilicity in the previous lectures

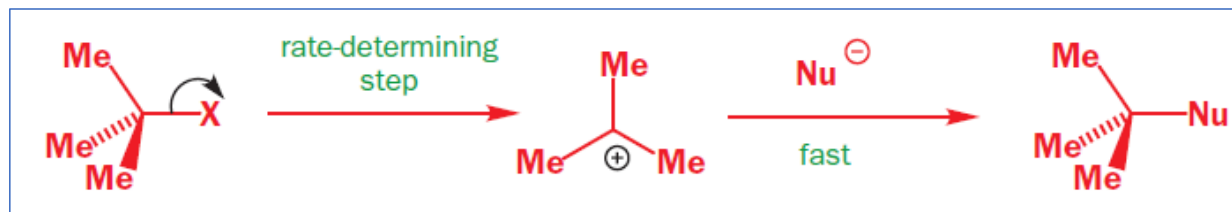
The leaving group

- What makes a leaving group good or bad?
 - Stability once it has left WITH a pair of electrons (resonance, solvation)
- Give some examples of bad leaving groups and some examples of good ones
- If the leaving group is too bad, then the substitution can't take place by either S_N1 or S_N2 .

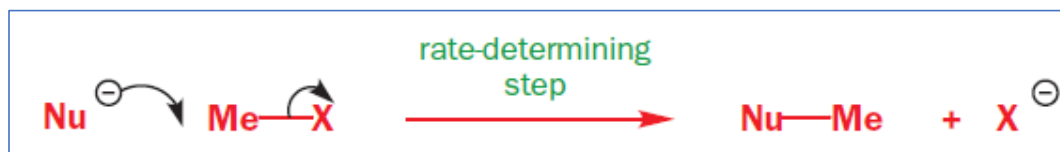
For example...



The leaving group



S_N1 reaction



S_N2 reaction

Halides as leaving group

- the strength of the C–halide bond
- the stability of the halide ion

- Iodide is the best leaving group among halides and fluoride is bad leaving group

Table 17.13 Halide leaving groups in the S_N1 and S_N2 reactions

Halide (X)	Strength of C–X bond, ¹ kJ mol ^{–1}	pK _a of HX
fluorine	118	+3
chlorine	81	–7
bromine	67	–9
iodine	54	–10

- Stable, and weak conjugate bases are good leaving groups

The leaving group

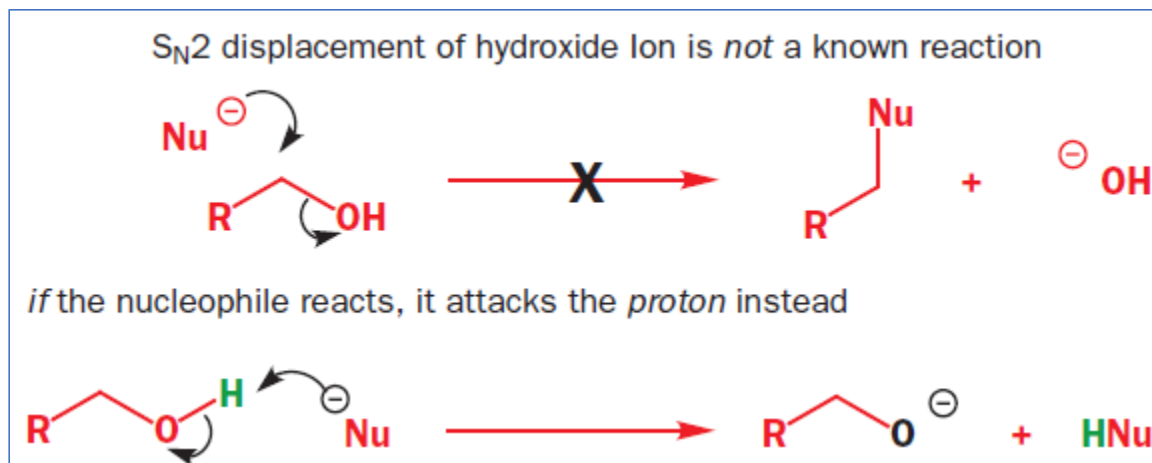
Table 6-4 Base Strengths and Leaving Groups

Conjugate acid		Leaving group		Conjugate acid		Leaving group	
<i>Strong</i>		<i>Good</i>		<i>Weak</i>		<i>Poor</i>	
HI (strongest)		I ⁻ (best)		HF		F ⁻	
HBr		Br ⁻		CH ₃ CO ₂ H		CH ₃ CO ₂ ⁻	
HCl		Cl ⁻		HCN		NC ⁻	
H ₂ SO ₄		HSO ₄ ⁻		CH ₃ SH		CH ₃ S ⁻	
H ₃ O ⁺		H ₂ O		CH ₃ OH		CH ₃ O ⁻	
CH ₃ SO ₃ H		CH ₃ SO ₃ ⁻		H ₂ O		HO ⁻	
				NH ₃		H ₂ N ⁻	
				H ₂ (weakest)		H ⁻ (worst)	

The leaving group

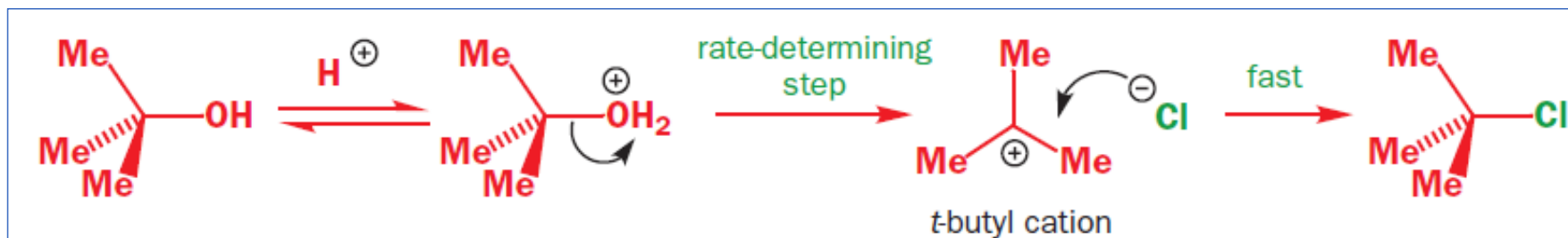
Alcohols as leaving group

- Hydroxide ion is very basic, very reactive, and a bad leaving group.
- If the nucleophile is more basic, it would remove a proton instead



In such a situation what would you do if you need to displace OH group?

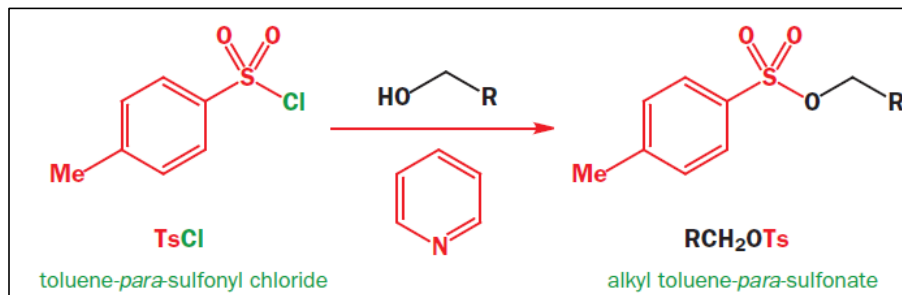
- The simplest answer is to protonate the OH group with strong acid



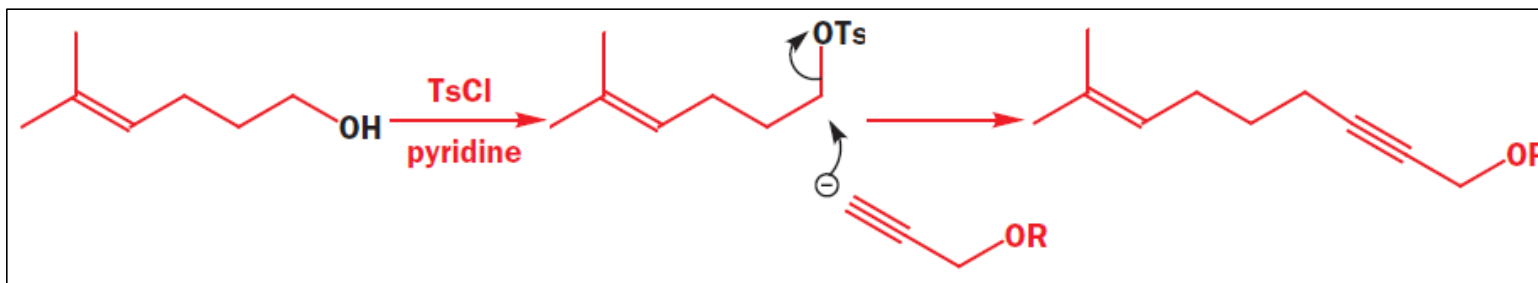
The leaving group

Alcohols as leaving group

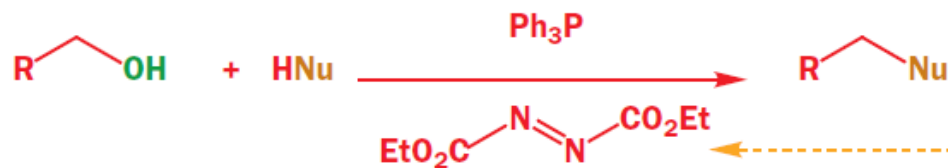
- to convert the OH group into a better leaving group by combination with an element that forms very strong bonds to oxygen



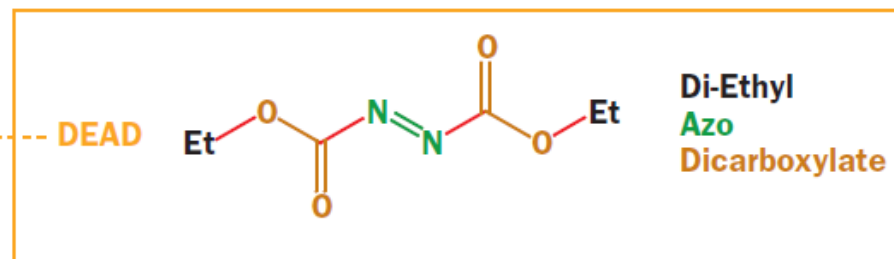
Converting to tosylates/mesylates



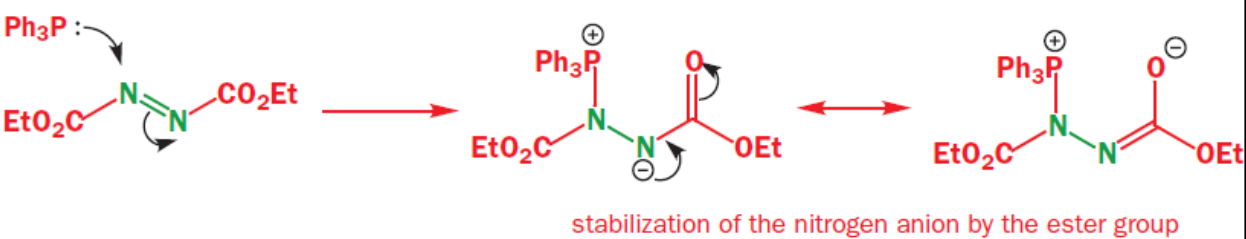
a Mitsunobu reaction



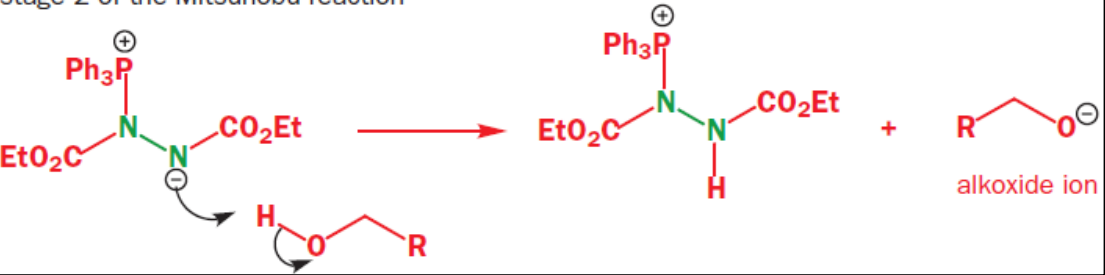
Mitsunobu reaction



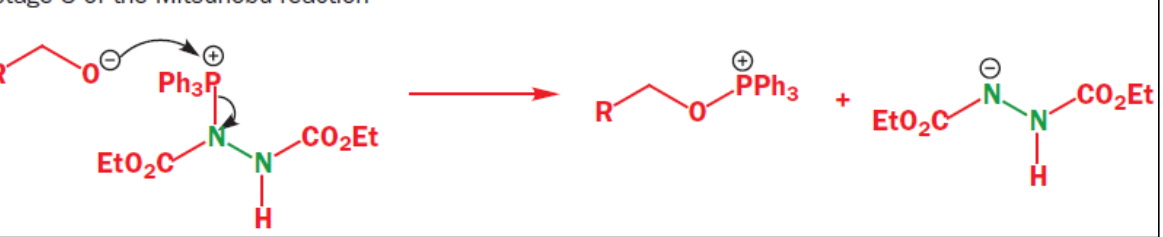
stage 1 of the Mitsunobu reaction



stage 2 of the Mitsunobu reaction



stage 3 of the Mitsunobu reaction



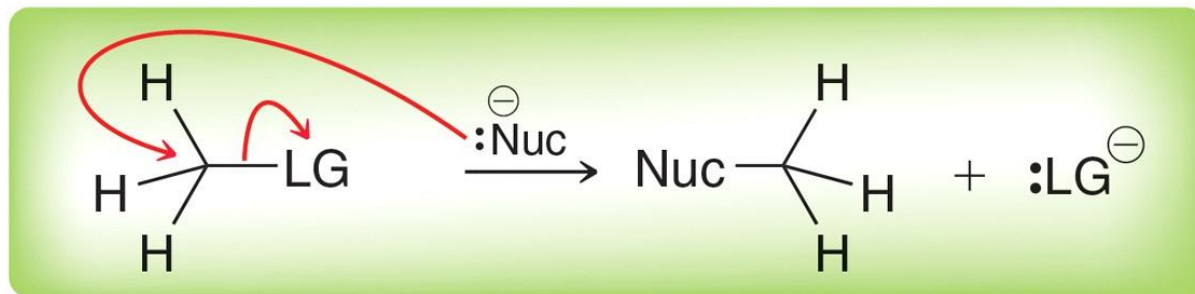
stage 4 of the Mitsunobu reaction



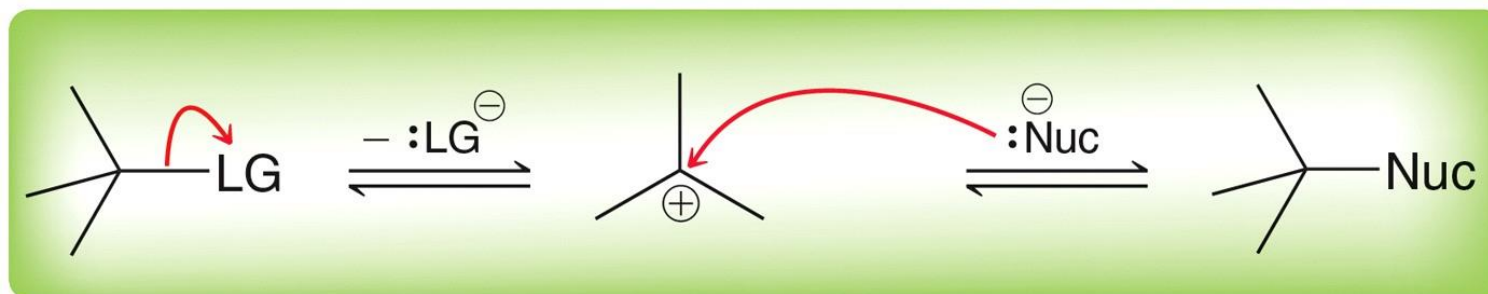
stage 5 of the Mitsunobu reaction



Solvent effects



S_N2 reaction

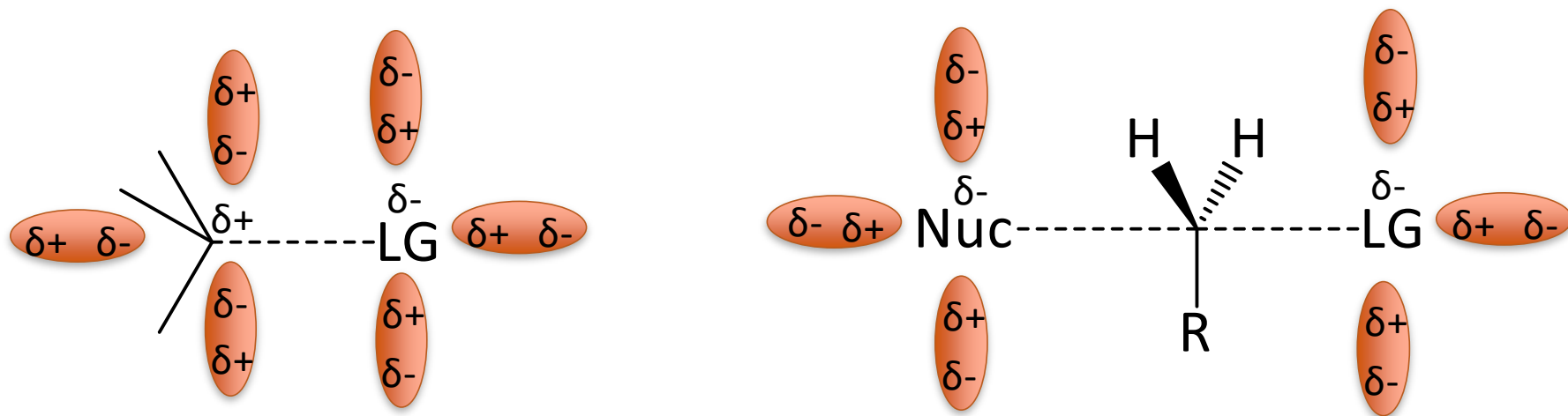


S_N1 reaction

- The solvent surrounds each species in the mechanism including the transition state.
- **How does that help to facilitate the reaction?**

Solvent effects

- The solvent ($\delta^+ \delta^-$) surrounds each species in the mechanism including the transition state



- To specifically promote S_N2 , what role should the solvent play?
 - The solvent should facilitate the collision between the nucleophile and the electrophile.
 - Is it possible that the solvent could interfere with that key collision?
- What type of solvent would you choose to accomplish this role?

Solvent effects

- Will this reaction be S_N1 or S_N2 ?

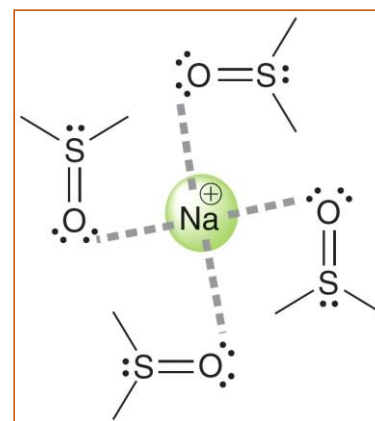
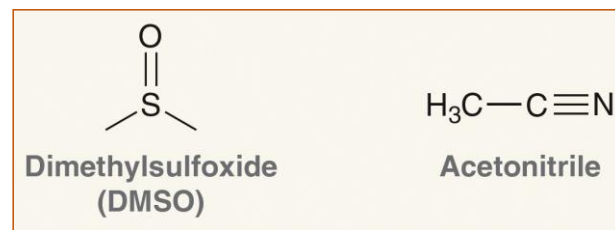


	CH ₃ OH	H ₂ O	DMSO	DMF	CH ₃ CN
Relative rate	1	7	1300	2800	5000
	Slowest rate				Fastest rate

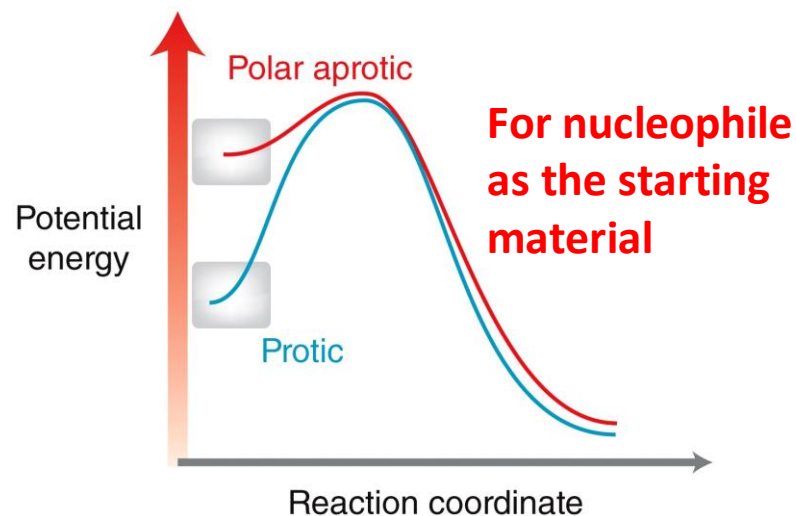
What do the highlighted red solvents have in common that makes them better than the others?

Solvent effects – S_N2 reaction

- To promote an S_N2, use a polar, aprotic solvent such as DMSO or acetonitrile
- Polar aprotic solvents can stabilize the counter-ion of the nucleophile leaving the nucleophile mostly **naked** and ready to attack the electrophile.
- Because a polar, aprotic solvent will not effectively solvate the nucleophile, the nucleophile is less stable and starts with a high potential energy
- The activation energy will be lower and the reaction faster

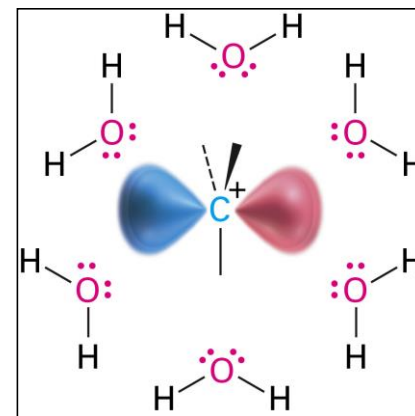
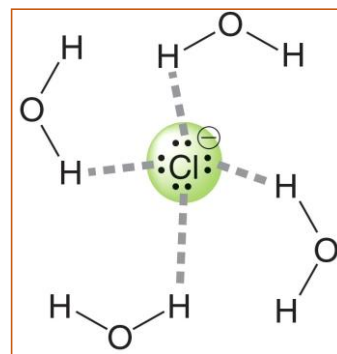
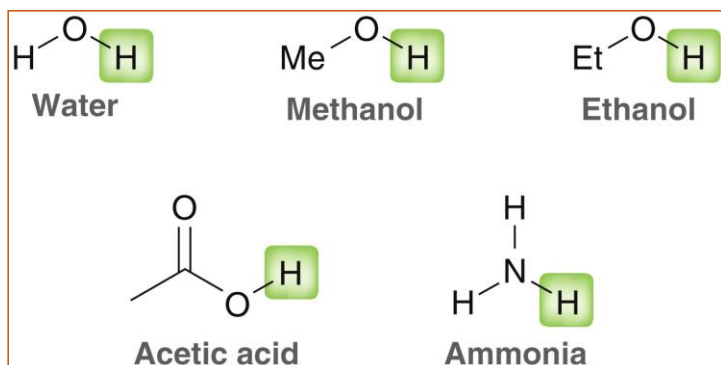


Ready to attack!

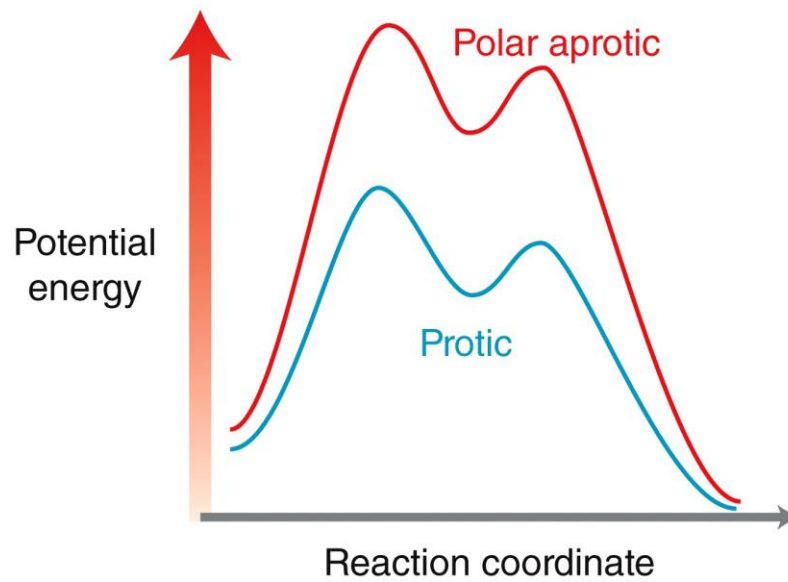


Solvent effects – S_N1 reaction

- To promote an S_N1, use a polar, protic solvent
- The protic solvent will Hydrogen bond with the nucleophile stabilizing it while the leaving group leaves first.



- A polar, protic solvent will also stabilize the full and partial charges that form during the S_N1 mechanism



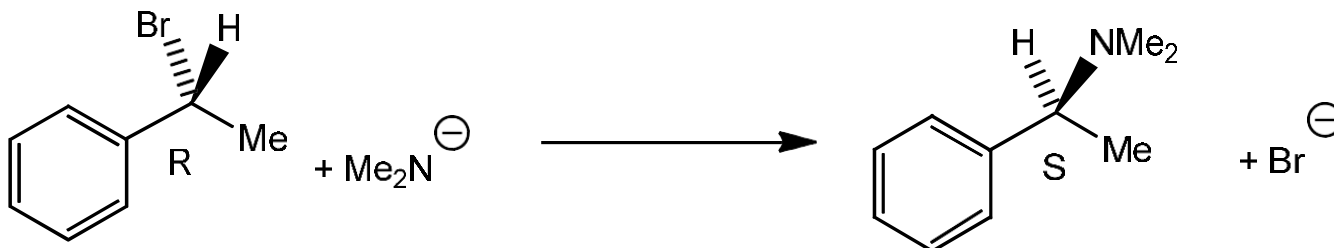
a. Write a mechanism and final product for the reaction between sodium ethoxide, $\text{NaOCH}_2\text{CH}_3$, and bromoethane, $\text{CH}_3\text{CH}_2\text{Br}$, in ethanol solvent, $\text{CH}_3\text{CH}_2\text{OH}$.

b. How would the preceding reaction be affected by each of the following changes?

1. Replace bromoethane with fluoroethane.
2. Replace bromoethane with bromomethane.
3. Replace sodium ethoxide with sodium ethanethiolate, $\text{NaSCH}_2\text{CH}_3$.
4. Replace ethanol with dimethylformamide (DMF).

The S_N stereochemistry

- Consider the following reaction

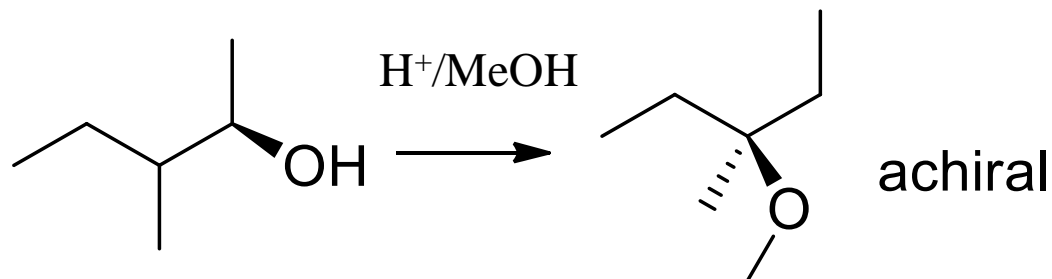


- What accounts for the inversion of product stereochemistry?
- Is the reaction reacting more by S_N1 or S_N2?

The S_N1 – Rearrangements

Rearrangements

- Rearrangements sometimes occur in S_N1 reactions
- After the leaving group leaves, the resulting carbocation **may** rearrange.

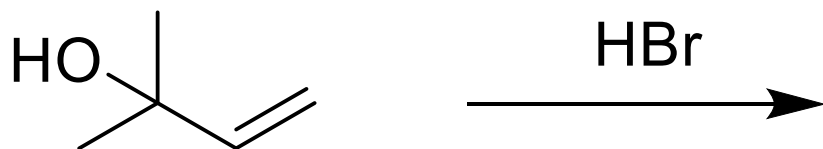
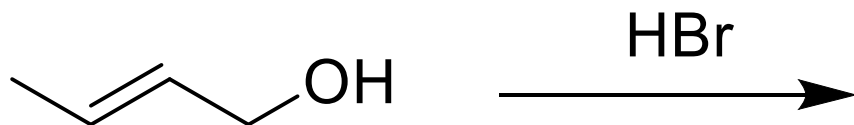
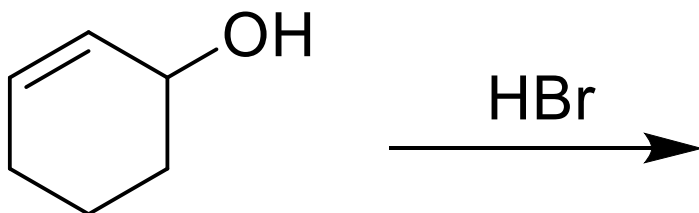


1. Draw a complete mechanism
2. Draw a complete reaction coordinate diagram including drawings for all transition states.

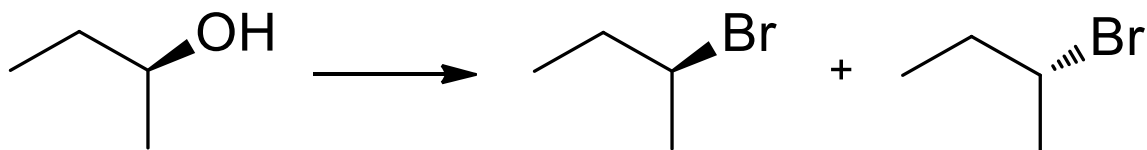
S_N1 vs. S_N2

- There are four main factors that determine whether a substitution reaction is more likely to occur by S_N1 or S_N2
- Lets examine them in order of importance
 1. The substrate (both sterics and the stability of the carbocation)
 2. The quality of the leaving group
 3. The strength of the nucleophile
 4. The solvent

Structure and stability of carbocations



- Propose reaction conditions and give a complete mechanism for the following substitution reaction



Write the plausible mechanism

Is it S_N1 or S_N2 ?

Identify the nucleophile and electrophile

