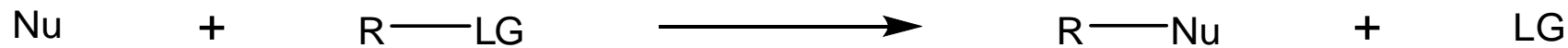


Substitution Reactions

Substitution reactions are reactions in which a nucleophile displaces an atom or group of atoms (the leaving group) from a **tetrahedral** carbon atom.

Consider the following general substitution reaction:



How might this reaction proceed?

We can imagine three different mechanisms:

- the nucleophile Nu-R bond forms first then the R-LG bond breaks.
- the Nu-R bond forms at the same time as the R-LG bond breaks.
- the R-LG bond breaks first then the Nu-R bond forms.

Are all these mechanisms reasonable?

The two mechanisms that are operative in substitution reactions are the S_N1 and S_N2 reactions.

- Reactions in which the leaving group leaves before the attack of the nucleophile are referred to as S_N1 reactions.
- Reactions in which the nucleophile attacks at the same time as the leaving group leaves are referred to as S_N2 reactions.

S stands for substitution

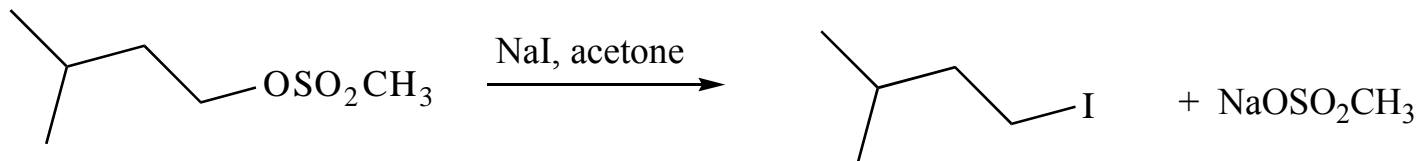
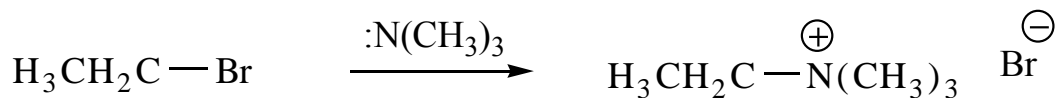
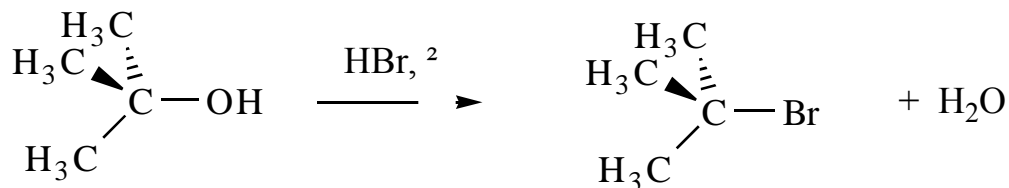
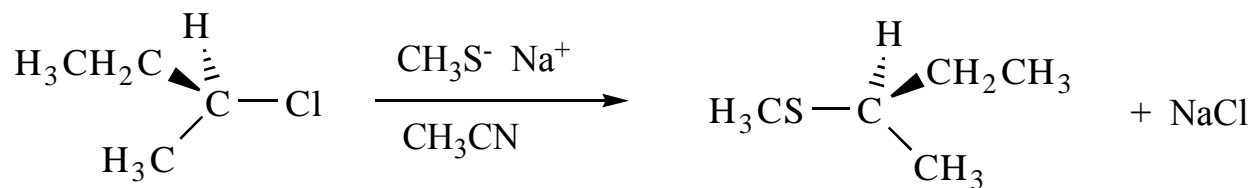
N stands for nucleophilic

The number refers to the number of reacting molecules *in the rate determining step*.

In substitution reactions the RDS is the step where the leaving groups leaves.

Consider the two different mechanisms for a substitution reaction. What factors would favour one pathway over the other?

Substitution Reactions of Alkyl Halides



All of these reactions:

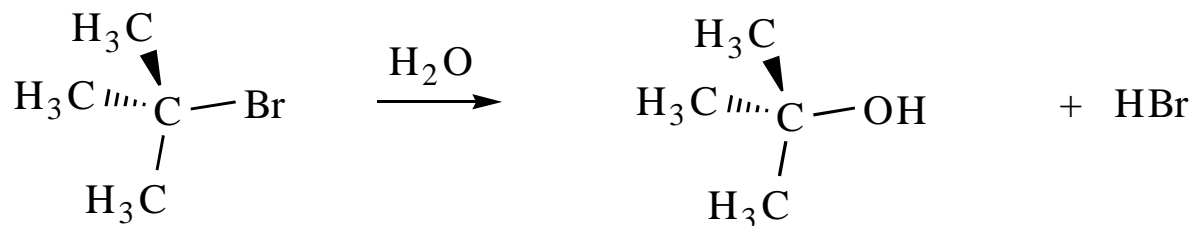
- involve displacement of a heteroatom from carbon -- the "leaving group"
- have a leaving group that is more EN than carbon making the carbon electrophilic
- have an electrophilic carbon that is sp^3 hybridized
- have a nucleophile present, which is either -ve or δ^-

Remember: Good leaving groups are weak bases!

Alkyl halides and alcohols S_N1 or S_N2 ?

- 3° , benzylic and allylic substrates undergo S_N1 reactions because THEY FORM RELATIVELY STABLE CARBOCATIONS.
- 1° , substrates undergo S_N2 reactions because they DO NOT FORM STABLE CARBOCATIONS and THE REACTION SITE IS STERICALLY ACCESSIBLE.
- 2° , substrates can undergo both types of reaction, but do so slowly.

The S_N1 Reaction



- S_N1 reactions in which the solvent participates as a nucleophile are called solvolysis reactions.

Substitution Reactions – S_N1

S_N1 reactions predominate when:

- A relatively stable carbocation is formed.
- The solvent is polar and protic.
- Weak nucleophile (e.g. a neutral molecule such as H₂O, ROH, etc.).

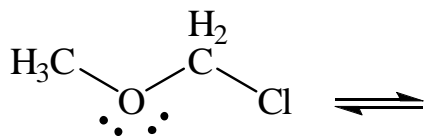
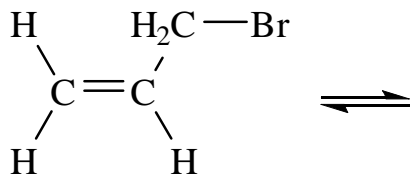
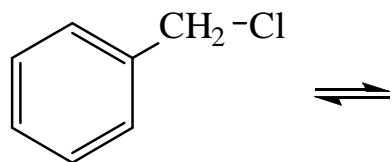
Carbocation Stability

Carbocation stability is dependent on:

- Coulombic stabilization
- Inductive stabilization
- Delocalization (resonance)
- Hyperconjugation.

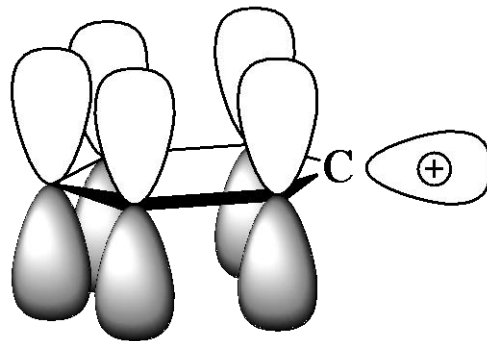
Carbocation Stability – Resonance Delocalization

Since S_N1 reactions involve carbocation intermediates, only those species that form reasonable carbocations will undergo this reaction in a timely fashion (this lifetime).

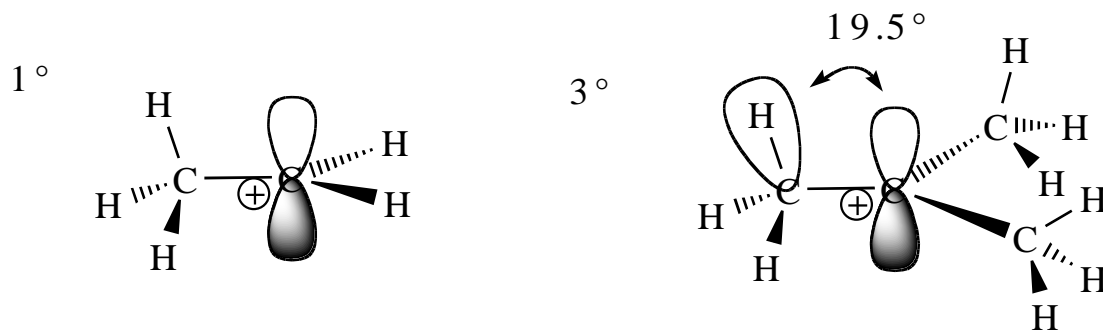


Carbocation Stability – Resonance Delocalization

- Aryl and vinyl carbocations **cannot** be stabilized by resonance. The empty orbital is orthogonal to the π -system and as such cannot be delocalized:



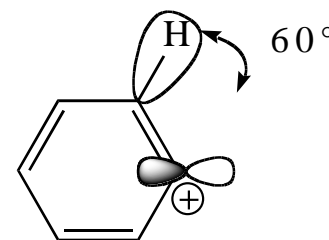
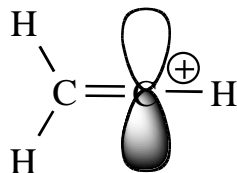
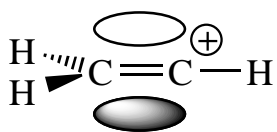
- Alkyl carbocations are also stabilized by electron donation from adjacent C–H bonds. This phenomenon is known as hyperconjugation.



- Recall that inductive and field arguments suggest carbocation stability is:



- Vinyl and aryl carbocations CANNOT be stabilized by resonance.



or by hyperconjugation!

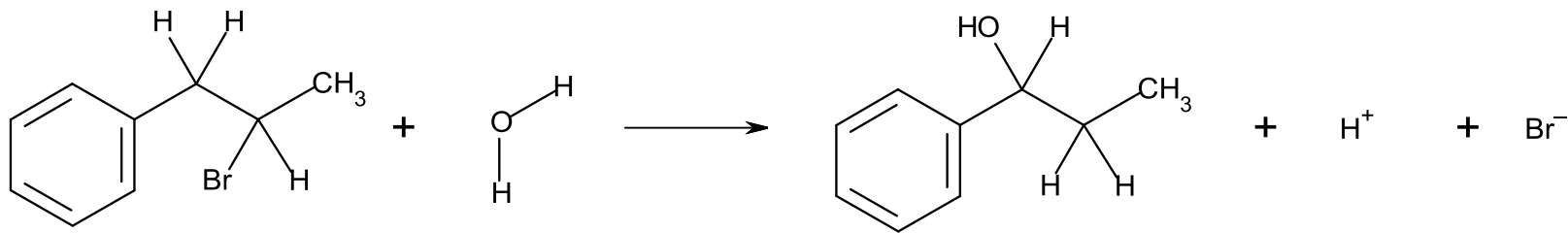
Thus, the order of carbonium ion stability is:

Benzylic ~ allylic > 3° > 2° > 1° > CH₃ > vinyl ~ aryl

- Usually, S_N1 reactions are practical for benzylic allylic and 3° substrates.

S_N1 - Rearrangements

- One consequence of reactions proceeding via carbocation intermediates is the occurrence of **rearrangement** side reactions. Consider the following reaction:

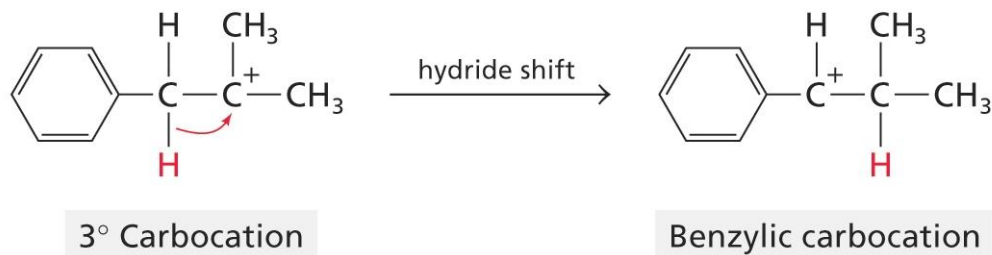
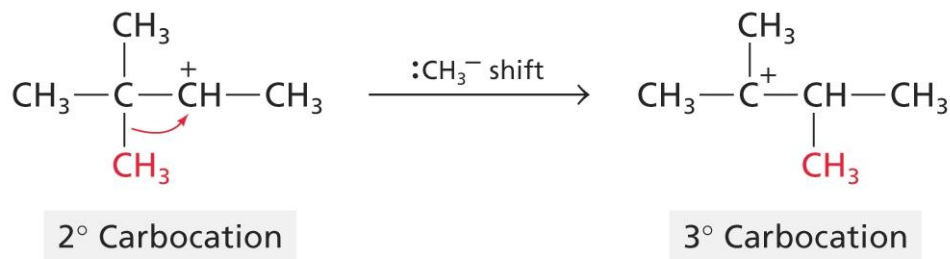
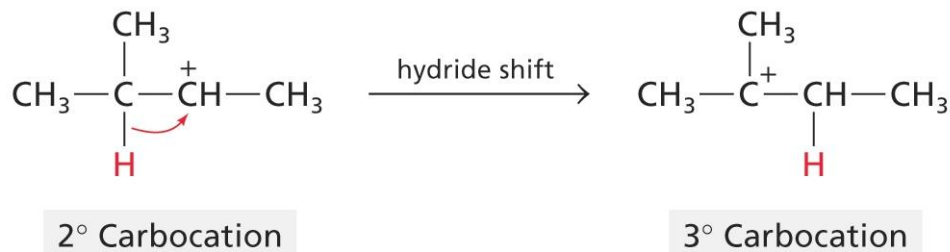


- The substitution product is a constitutional isomer of the product expected. Propose a mechanism for the above reaction:

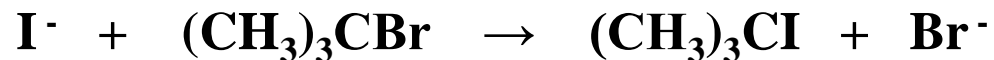
S_N1 - Rearrangements

It is worth noting that carbocation rearrangements can involve shifting either a hydride ion or a methyl anion. In either case, you will always be forming a more stable carbocation.

Pay close attention to the way curly arrows are drawn when proposing a hydride or methyl shift. We should be able to tell if you are proposing a hydride shift or generation of a pi bond.



The S_N1 Reaction - Kinetics.

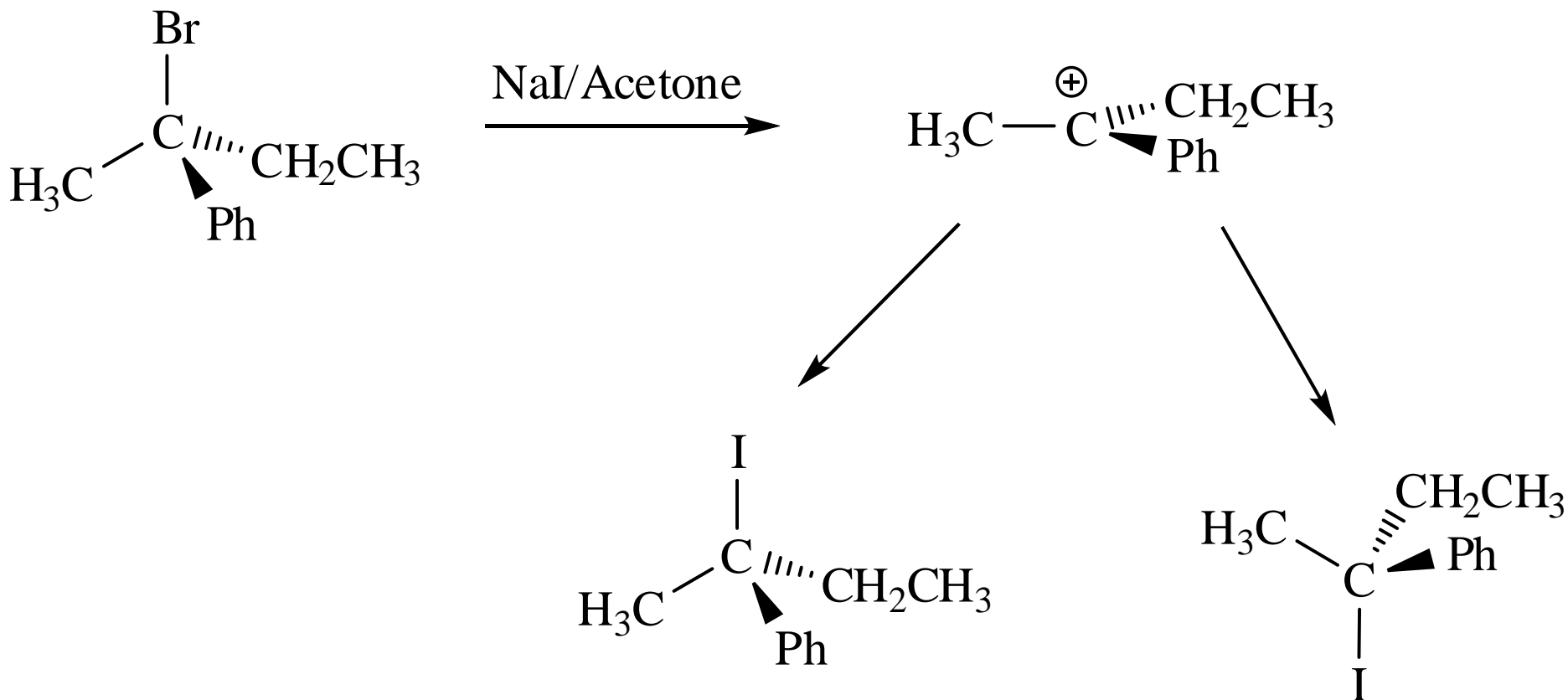


Consider:

- What happens to the rate of production of (CH₃)₃CI if the concentration of I⁻ is held constant and the concentration of (CH₃)₃CBr is increased?

- What happens to the rate of production of (CH₃)₃CI if the concentration of (CH₃)₃CBr is held constant and the concentration of I⁻ is increased?

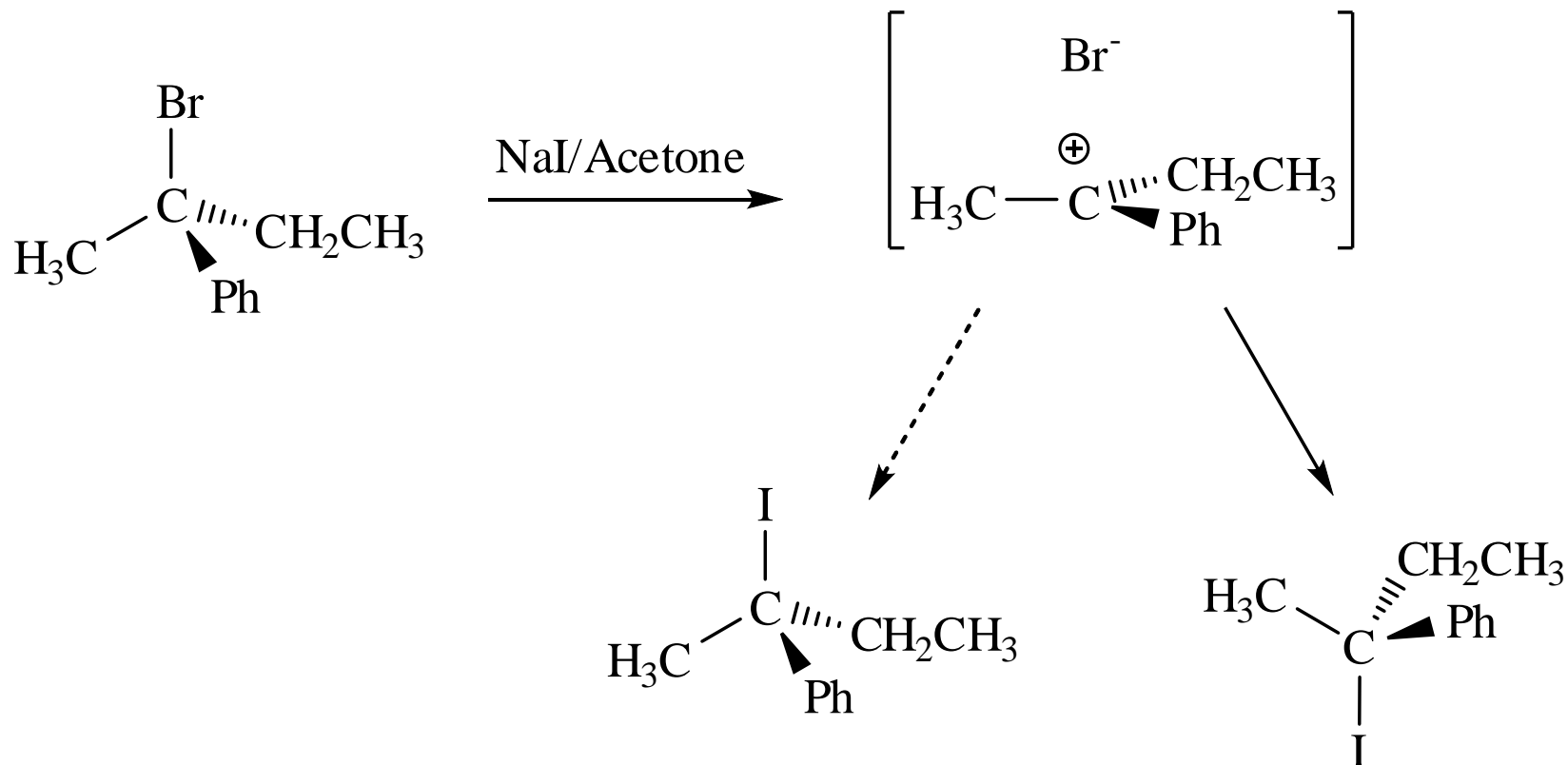
The Stereochemistry of the S_N1 reaction



- The nature of the intermediate is such that the nucleophile can attack from either side with equal likelihood.
- Reactions in which the configuration of a chiral centre is scrambled are said to occur with RACEMIZATION.

The Stereochemistry of the S_N1 reaction

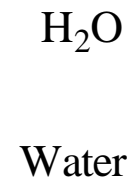
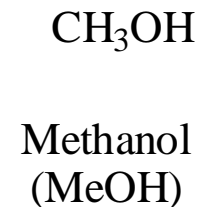
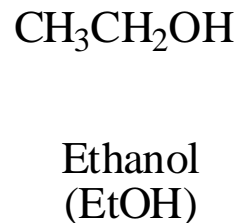
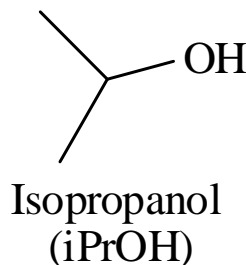
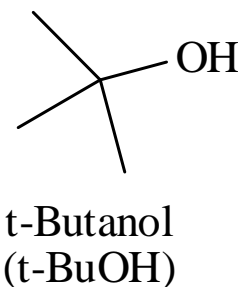
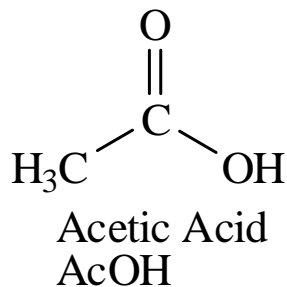
Sometimes (depending on conditions) reactions occur with only partial racemization.



S_N1 reactions – Solvent Effects

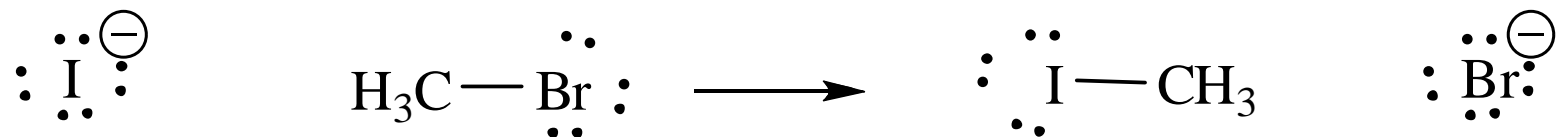
- S_N1 reactions are typically done in **polar protic** solvents. Polar protic solvents are used because they help stabilize the transition state during the process of forming the carbocation intermediate. The more stabilized the transition state, the faster the carbocation will form.

Some common **polar protic** solvents:



The S_N2 Reaction.

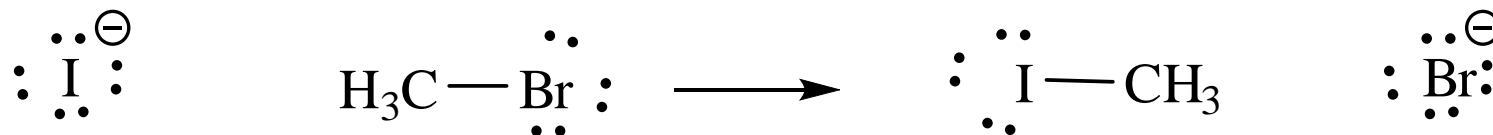
The S_N2 reaction is favoured for 1° and methyl substrates.



Sketch a reaction profile diagram for the above reaction.



The S_N2 Reaction - Kinetics.



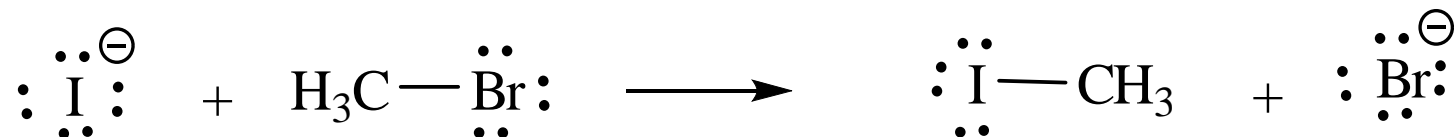
Consider:

- What happens to the rate of production of CH₃I if the concentration of CH₃Br is held constant and the concentration of I⁻ is increased?

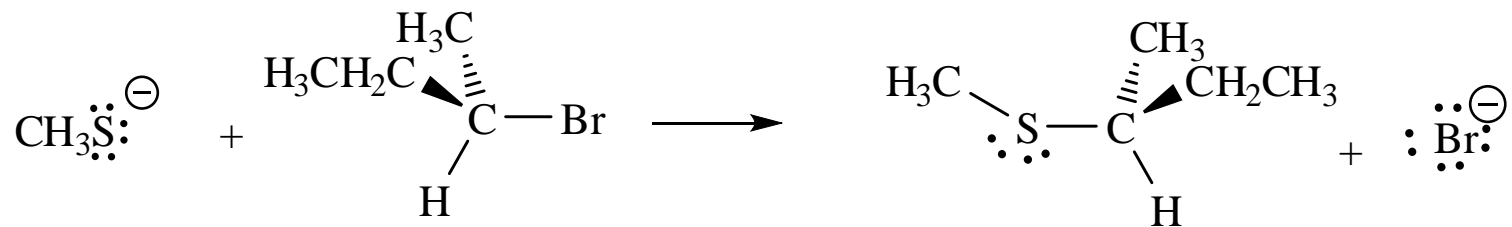
- What happens to the rate of production of CH₃I if the concentration of I⁻ is held constant and the concentration of CH₃Br is increased?

The Stereochemistry of the S_N2 reaction

The reaction geometry is such that the collision must occur with the nucleophile attacking the back side of the C—LG bond.



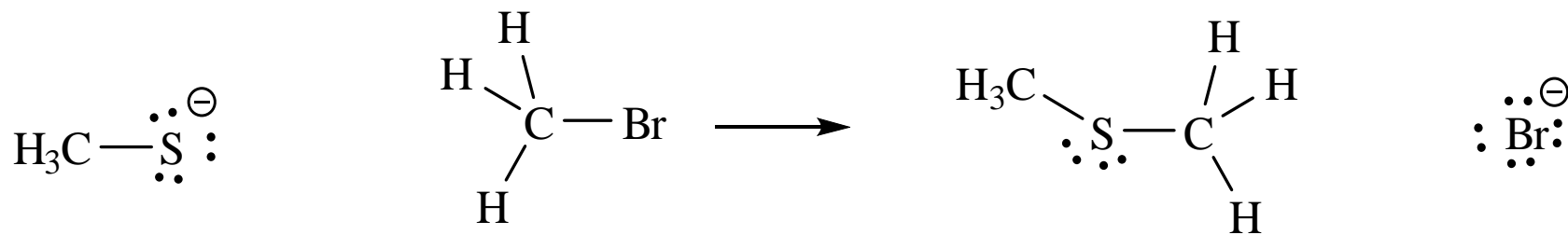
When attack occurs at an asymmetric carbon, the reaction occurs **exclusively** with inversion of the absolute stereochemistry.



Stereospecific: A reaction in which the mechanism dictates that different stereoisomeric reactants give different stereoisomeric products.

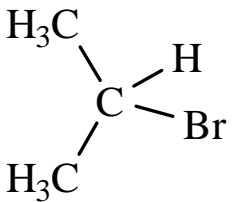
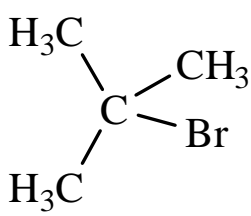
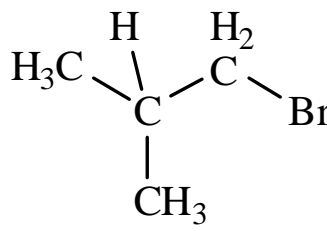
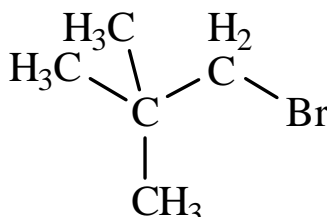
The Stereochemistry of the S_N2 reaction

Why backside attack?



S_N2 reactions - Reactivity

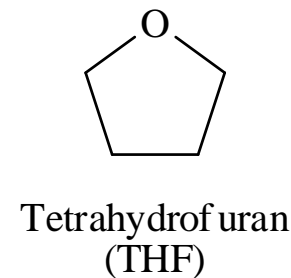
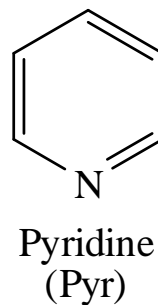
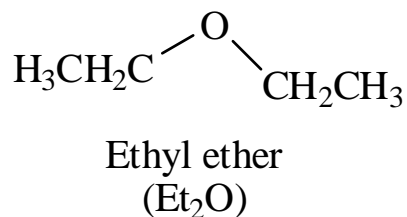
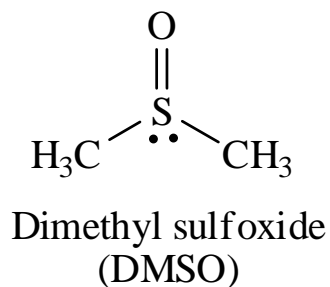
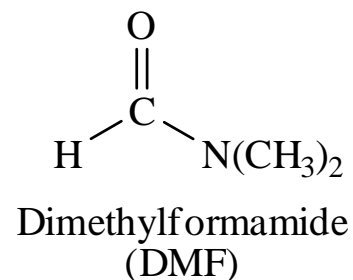
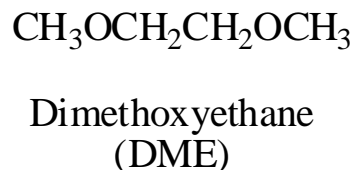
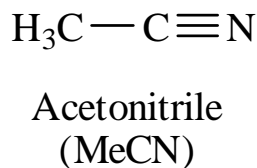
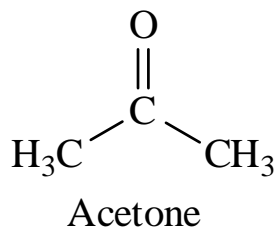
Substrate dependence:

Substrate	Relative rate	Substrate	Relative rate
CH ₃ Br	100	CH ₃ Br	100
CH ₃ CH ₂ Br	1.31	CH ₃ CH ₂ Br	1.31
CH ₃ CH ₂ CH ₂ Br	0.81	CH ₃ CH ₂ CH ₂ Br	0.81
	0.015	CH ₃ CH ₂ CH ₂ CH ₂ Br	0.52
	0.004		0.052
			0.00001

S_N2 reactions – Solvent Effects

S_N2 reactions are typically done in **polar aprotic** solvents. These solvents are polar enough to solubilize the nucleophile but do not stabilize the nucleophiles enough to prevent reaction.

Some common **polar aprotic** solvents:

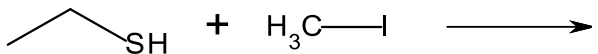
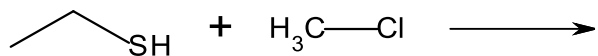


S_N2 reactions - Reactivity

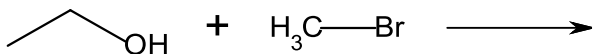
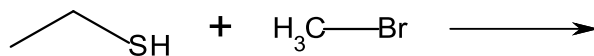
When evaluating S_N2 reactions, you have to consider everything involved in the reaction. This includes the substrate, the nucleophile, the leaving group and the solvent.

For each set of reactions, draw the S_N2 products. Then indicate which reaction should proceed faster and why.

A



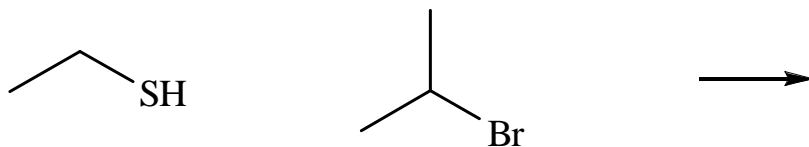
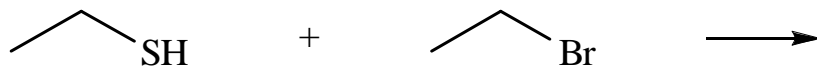
B



S_N2 reactions - Reactivity

For each set of reactions, draw the S_N2 products. Then indicate which reaction should proceed faster and why.

C



S_N1 vs. S_N2 reactions – Comparison

S_N2

S_N1

	S_N2	S_N1
Reaction Order	second order reaction	first order reaction
Minimum # Steps	1 or more steps	2 or more steps
Intermediates?	No	carbocation
Stereochemical Consequences	stereospecific inversion of configuration at electrophilic site	racemization (full or partial) at electrophilic site
Importance of Nucleophile Strength	very important; no reaction for weak nucleophiles like H_2O	unimportant
Importance of Leaving Group	very important; no reaction for weak leaving groups like HO^-	very important; no reaction for weak leaving groups like HO^-
Substrate Structure Dependence	avoid steric hindrance; $CH_3 > 1^\circ > 2^\circ(\text{slow}) > 3^\circ$ (no); no reaction for aryl/vinyl	need carbocation stabilization; $3^\circ > 2^\circ$ (slow) $> 1^\circ$ (no); resonance stabilization helps; no reaction for aryl/vinyl
Solvent	polar aprotic	polar protic
Competing Reactions	E2	E1, E2, rearrangement

S_N1 vs. S_N2 reactions

- Would you expect the following reactions to proceed via S_N1 , S_N2 , both, or neither? Draw the expected product(s) for each reaction.

