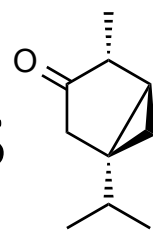


Chemistry 2600

Chapter 11

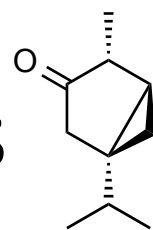
Displacement Reactions on Saturated Carbons

Nucleophilic Displacement Reactions

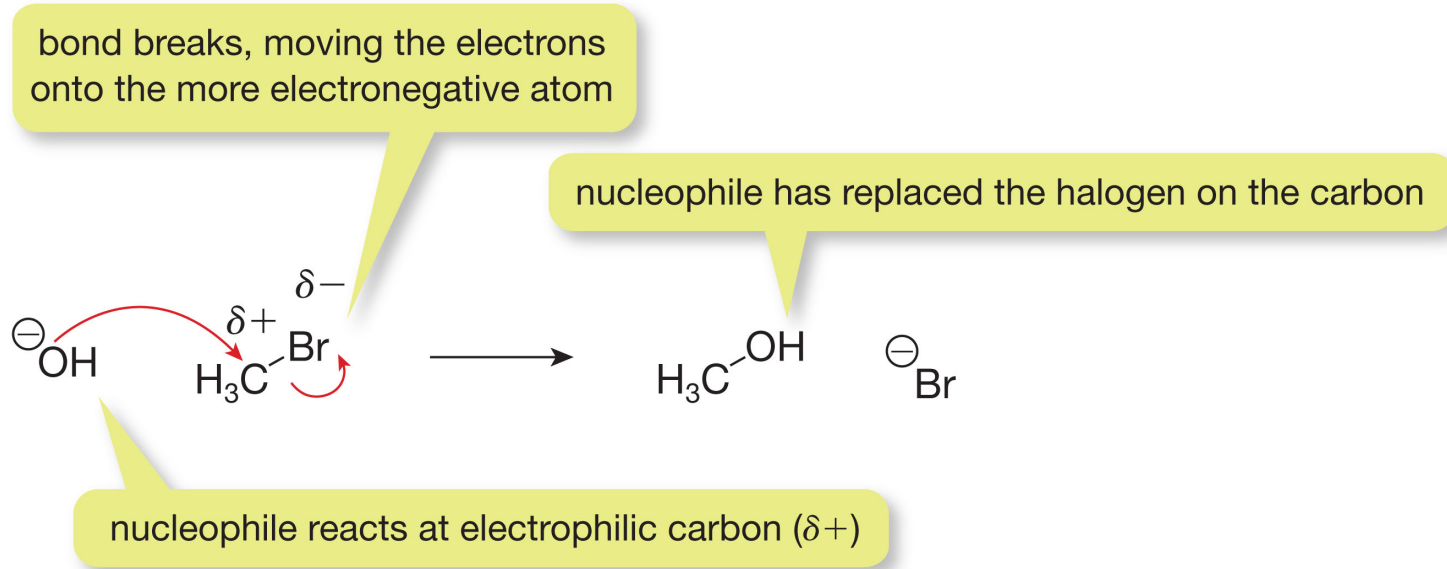


- ***Nucleophilic displacement*** reactions are those in which a nucleophile (Nu) displaces an atom/group in a molecule.
- In alkyl halides, the carbon-halide bond is polarized toward the more electronegative halogen atom, creating a partial (+) charge at the α -carbon atom, the electrophile (E).
- When nucleophiles react with an alkyl halide, they attack this electrophilic carbon atom and displace the halogen atom. This is called a ***nucleophilic substitution reaction***.

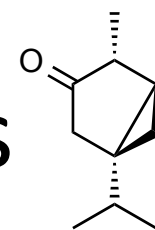
Nucleophilic Displacement Reactions



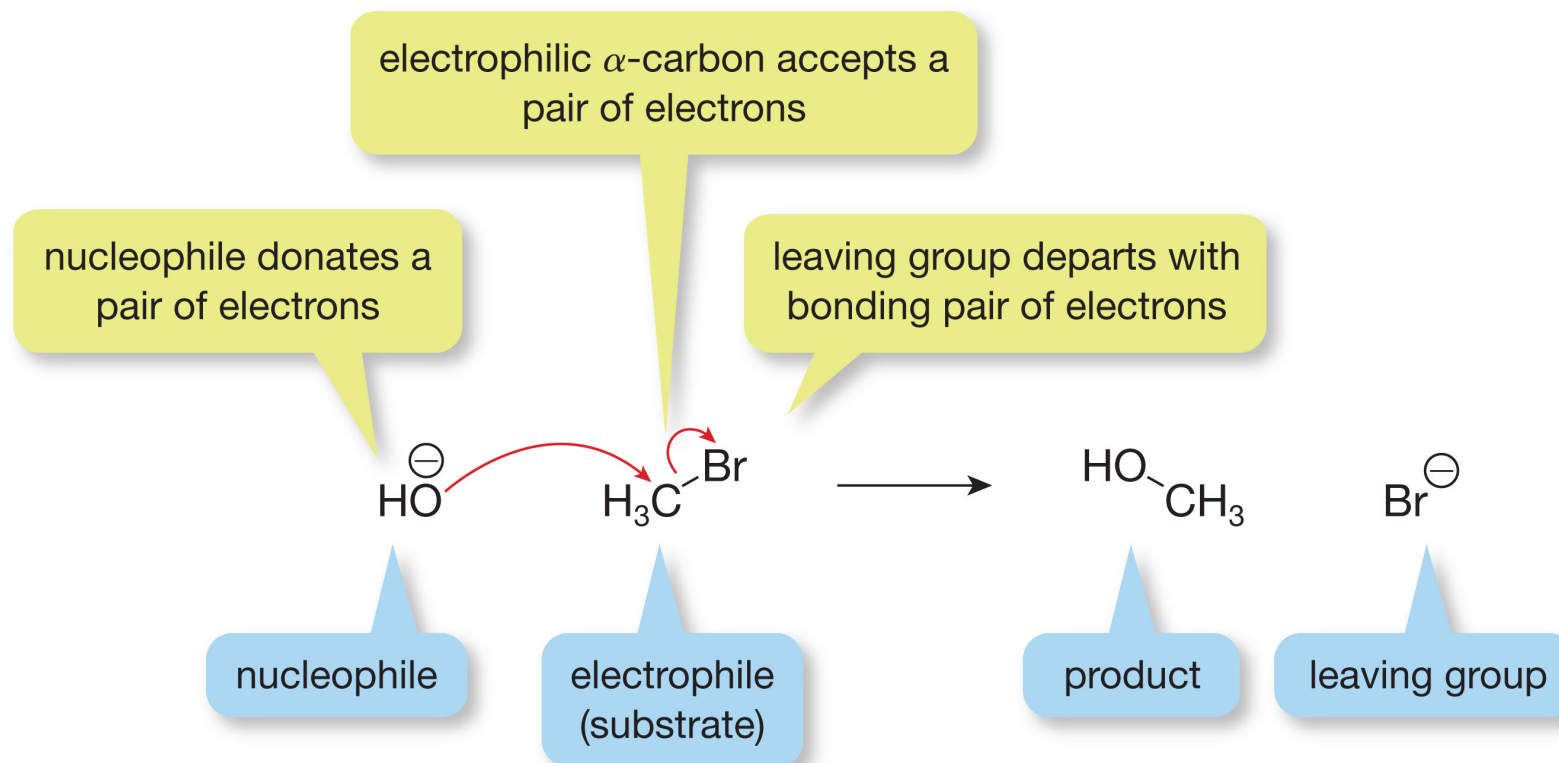
- The nucleophile uses a lone pair to form a new bond to the carbon atom. At the same time, the carbon-halogen bond breaks.
- The net result is the nucleophile substitutes the halogen.



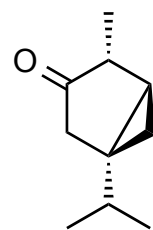
Nucleophilic Displacement Reactions



- The components of a substitution reaction.



Reaction Rates of S_N2 Reactions



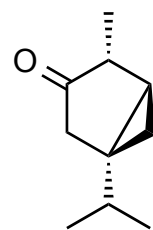
- For the reaction of HO⁻ + CH₃Br, the rate of the reaction is described by the following expression called the rate law:

$$\text{rate} = k [\text{OH}^{\ominus}][\text{CH}_3\text{Br}]$$

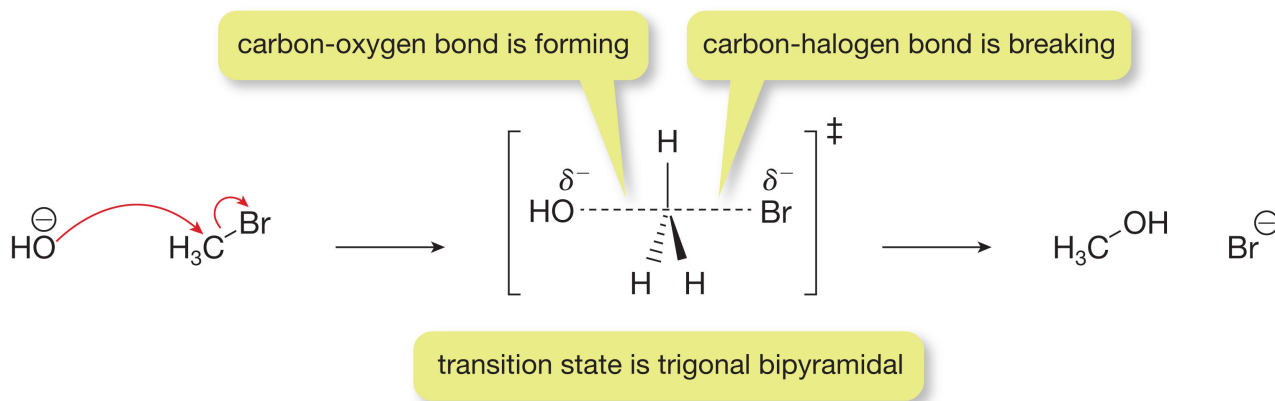
the rate of an S_N2 reaction depends on the concentration of both the nucleophile and the electrophile

- Experiments show that the rate of this reaction is dependent on the concentration of **both** the nucleophile (HO⁻) and the electrophile (CH₃Br).
- This type of reaction is designated S_N2 (substitution, nucleophilic, bimolecular)

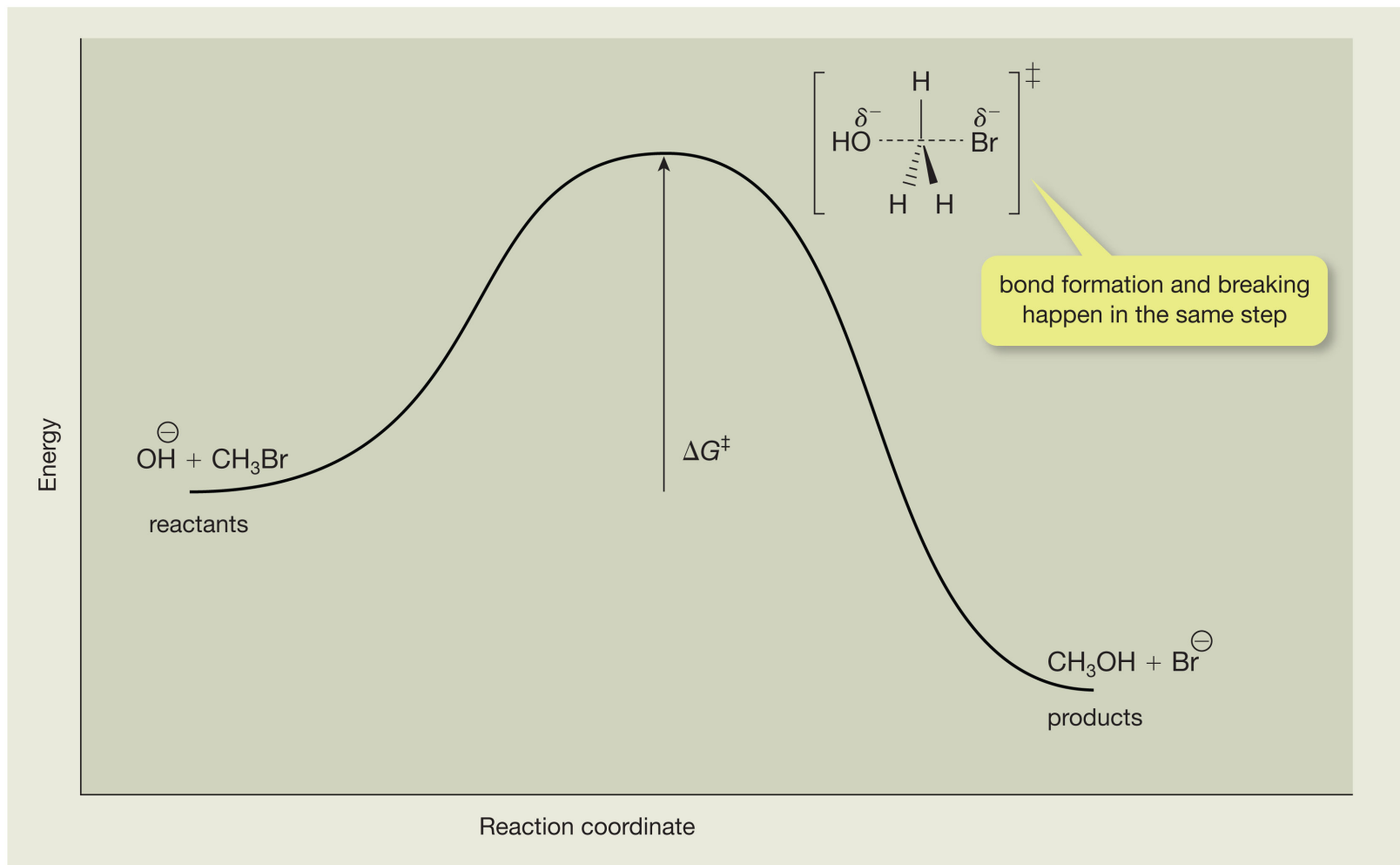
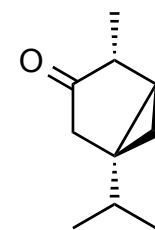
Reaction Rates of S_N2 Reactions



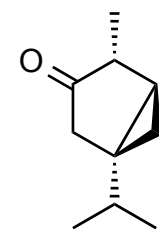
- Bimolecular refers to 2 reactants involved in the rate determining step (RDS). For substitution reactions, the RDS is when the leaving group leaves.
- Because both the Nu and E are both involved in the RDS, bond formation and bond breaking must occur in the same step. We describe this as a **concerted reaction**.



Reaction Rates of S_N2 Reactions



Reaction Rates of S_N2 Reactions

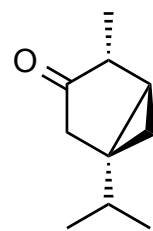


- Because there are two reactant molecules in the RDS in an S_N2 reaction, we say that it is ***second order***.
- The rate of the reaction is generally measured as the change in the concentration of one reactant or the product over a given unit of time.

$$\text{average rate} = - \frac{\Delta[\text{reactant}]}{\Delta t}$$

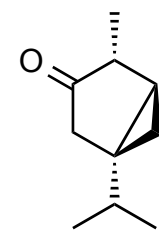
$$\text{average rate} = \frac{\Delta[\text{product}]}{\Delta t}$$

Reaction Rates of S_N2 Reactions



- What happens to the rate of production of CH₃OH if the concentration of CH₃Br is held constant and the concentration of OH⁻ is increased?
- What happens to the rate of production of CH₃OH if the concentration of OH⁻ is held constant and the concentration of CH₃Br is increased?
- A mechanism is a hypothesis that must be in agreement with all observed rate data.
- We can use rate data to test whether or not a given reaction might proceed via an S_N2 mechanism.

Reaction Rates of S_N2 Reactions

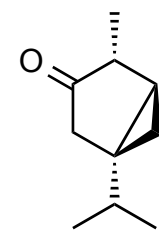


- The substitution reaction between bromomethane and hydroxide is studied, giving the following rate data:

$[\text{CH}_3\text{Br}]$ (M)	$[\text{HO}^-]$ (M)	Initial Rate (M/s)
0.1	0.1	0.15
0.2	0.1	0.31
0.2	0.2	0.63

- Determine the rate law for this reaction. Calculate k . Might this reaction proceed via an S_N2 mechanism?

Reaction Rates of S_N2 Reactions

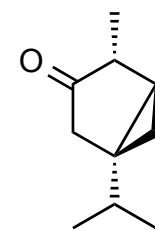


- The substitution reaction between 2-chloro-2-methylpropane and water is studied, giving the following rate data:

$[(\text{CH}_3)_3\text{CCl}]$ (M)	$[\text{H}_2\text{O}]$ (M)	Initial Rate (M/s)
0.1	0.1	0.0068
0.2	0.1	0.014
0.2	0.2	0.014

- Determine the rate law for this reaction. Calculate k . Might this reaction proceed via an S_N2 mechanism?

Mechanisms for S_N2 Reactions



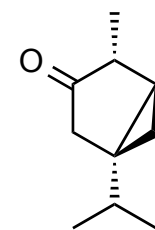
- The primary step in S_N2 reactions is nucleophilic attack of the electrophile. This may be preceded or followed by a proton transfer step, depending on the nature of the nucleophile (charged or neutral).

reaction happens in one step

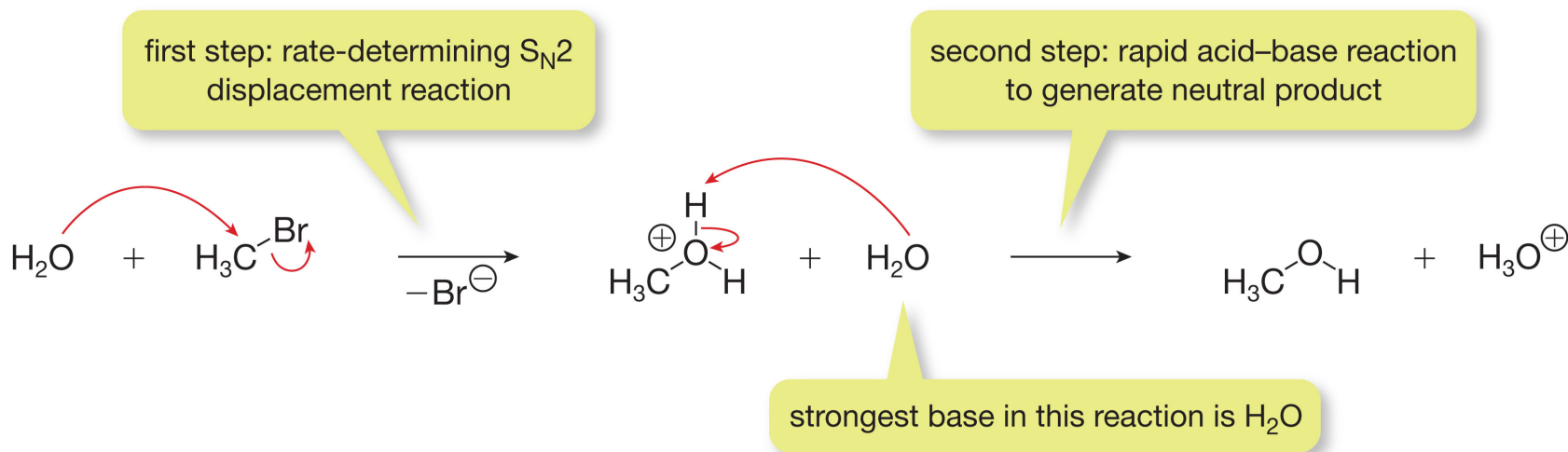


from deprotonation of CH₃OH

Mechanisms for S_N2 Reactions

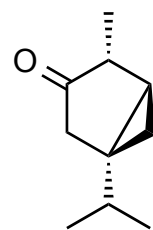


- The primary step in S_N2 reactions is nucleophilic attack of the electrophile. This may be preceded or followed by a proton transfer step, depending on the nature of the nucleophile

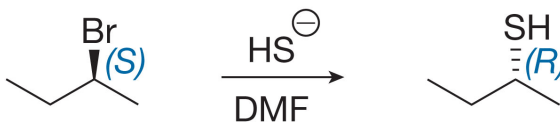


- Regardless of the charge on the Nu, the RDS is still the displacement step.

Stereochemistry of S_N2 Reactions



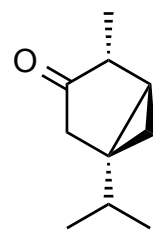
- S_N2 reactions proceed via inversion of configuration of the α -carbon.



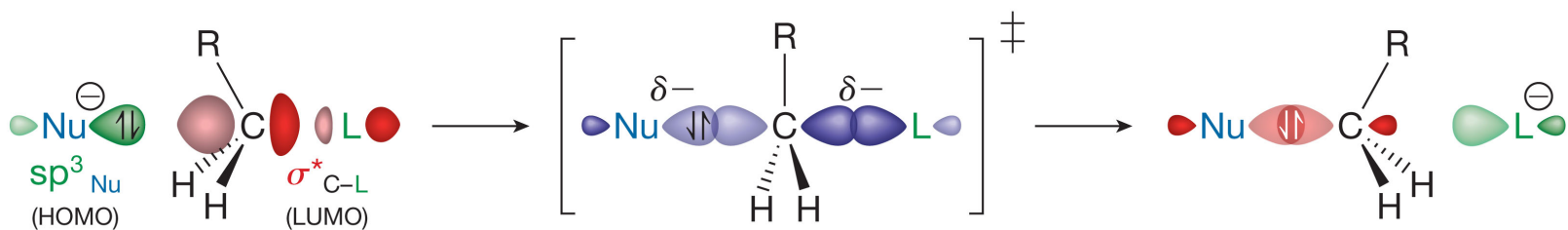
nucleophile inverts the configuration at the α -carbon during S_N2 reactions

- This inversion is analogous to an umbrella flipping in the wind.
- In order for this to occur, the nucleophile approached the α -carbon from the opposite side (backside) of the leaving group.

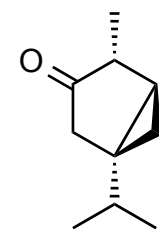
Stereochemistry of S_N2 Reactions



- Two factors accounts the nucleophile's approach:
 - Front side attack is impeded by the leaving group.
 - Backside attack allows the filled orbital (HOMO) of the nucleophile to overlap with the empty orbital (LUMO) of the electrophile.

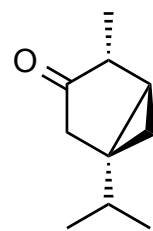


Nucleophilicity in S_N2 Reactions



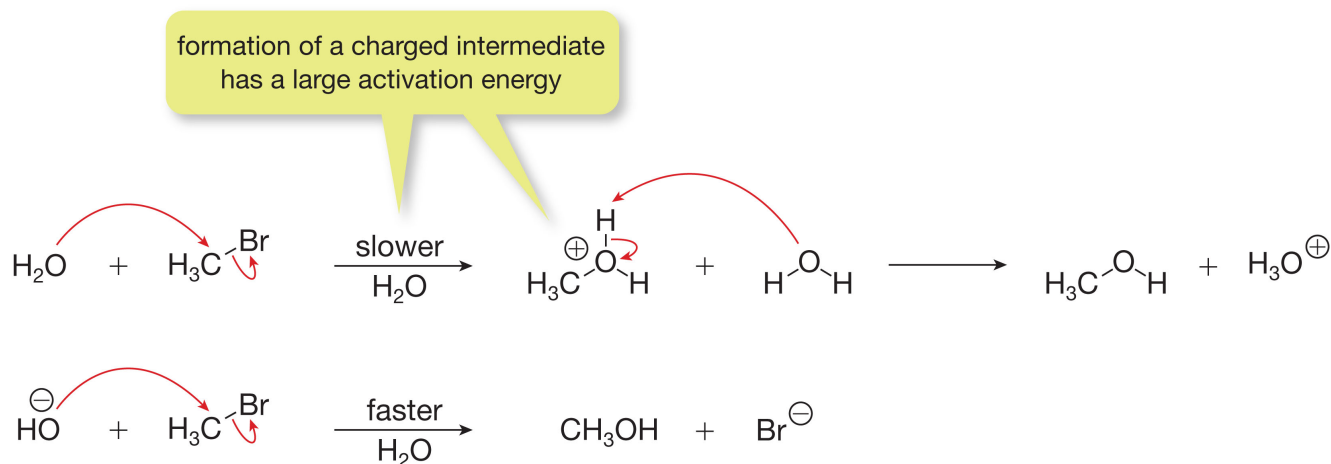
- Several factors can affect the rate of the SN2 reactions.
- The most important is the ability of the nucleophile to donate electrons – this refers to its **nucleophilicity**.
- Nucleophilicity is a **kinetic** property and is an expression of **how fast** a nucleophile is able to react.
- Nucleophilicity is dependent on the following:
 - Charge
 - Electronegativity
 - Atom size
 - Electron delocalization
 - Sterics

Nucleophilicity in S_N2 Reactions

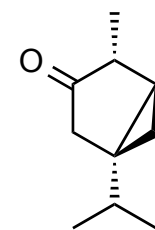


Effect of Negative Charge:

- Negatively charged species have more available electrons than neutral species, so they are better electron donors.
- Since bases are by definition 'electron donors', some bases are also strong nucleophiles.
- Do not confuse bases with nucleophiles.



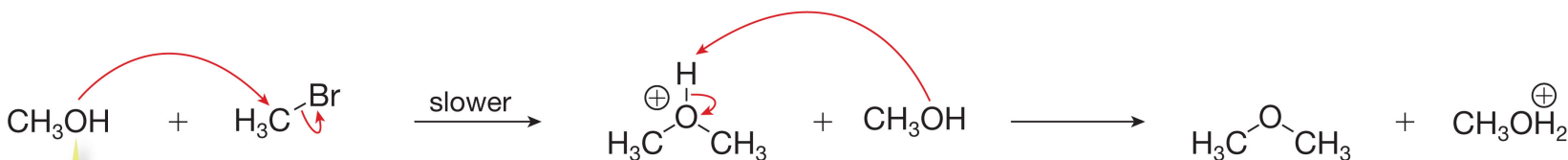
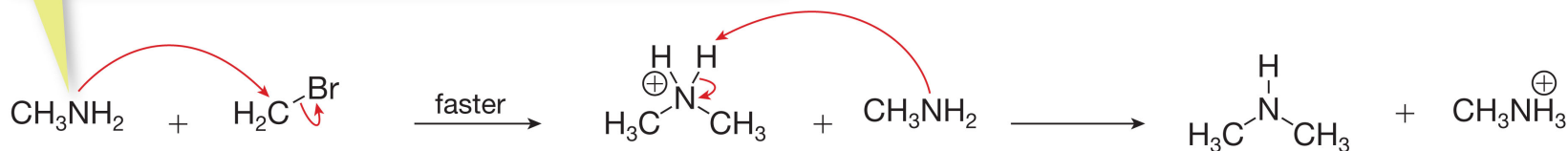
Nucleophilicity in S_N2 Reactions



Effect of Electronegativity:

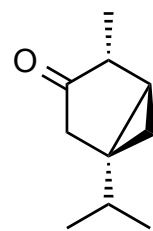
- Atoms with higher electronegativity are less nucleophilic because they are less able to share their valence electrons to make a bond.

nitrogen is less electronegative and is a better electron donor



oxygen is more electronegative and is a weaker electron donor

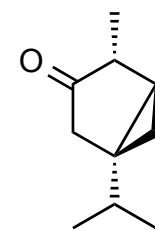
Nucleophilicity in S_N2 Reactions



Effect of Atomic Size:

- As atoms increase in size, the valence electrons are further and more shielded from the nucleus, therefore, the effective attraction to the nucleus is reduced.
- Such atoms are said to be ***polarizable***.
- These atoms have large, diffuse electron clouds, which are easily distorted by nearby charges.

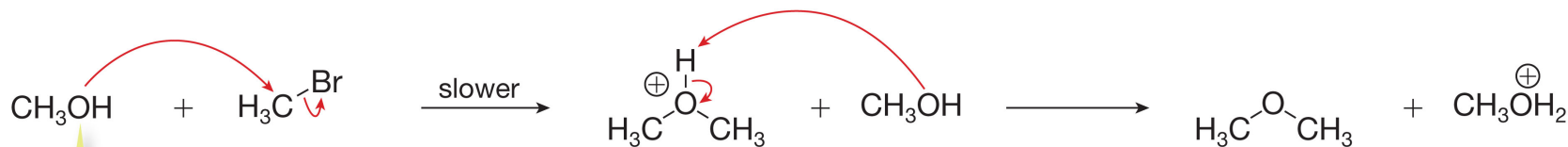
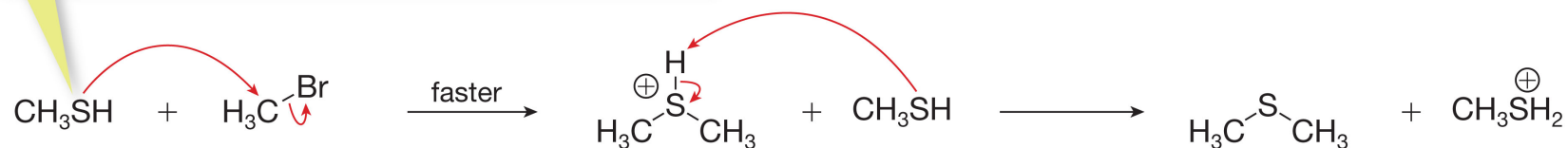
Nucleophilicity in S_N2 Reactions



Effect of Atomic Size:

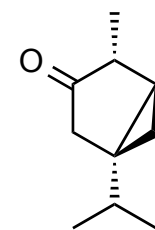
- Larger atoms are more nucleophilic than smaller atoms because they can donate electrons more easily.

sulfur is more polarizable and is a better electron donor



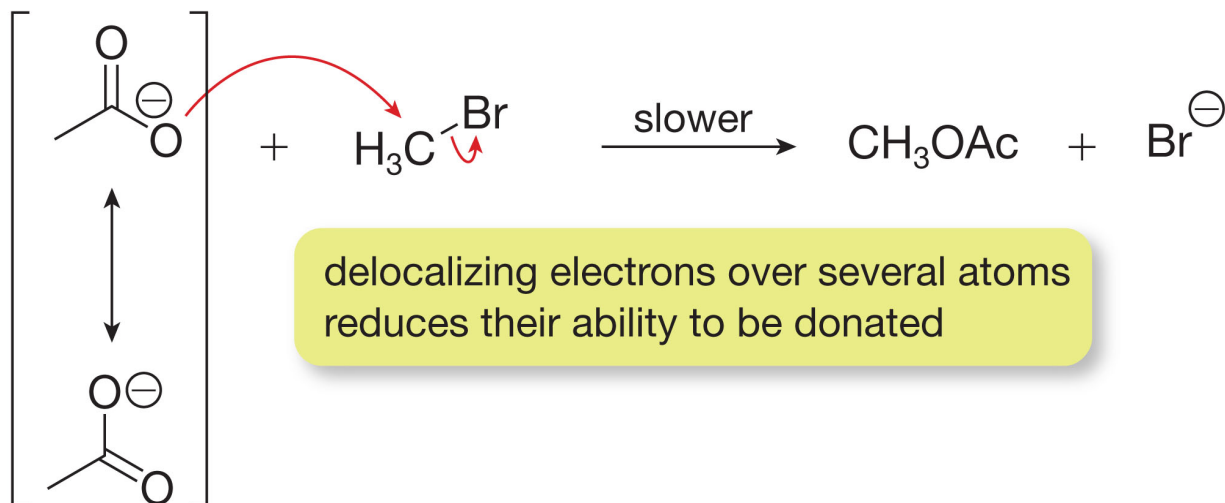
oxygen is less polarizable and is a weaker electron donor

Nucleophilicity in S_N2 Reactions



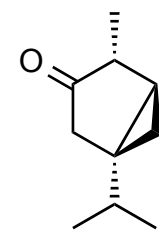
Effect of Electron Delocalization:

- Because delocalized electrons are shared over several atoms, they are less readily donated and therefore less nucleophilic.



delocalizing electrons over several atoms reduces their ability to be donated

Nucleophilicity in S_N2 Reactions



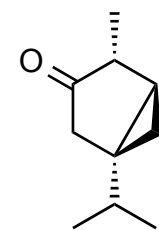
Effect of Steric Congestion:

- Large groups around the nucleophilic atom impairs its nucleophilicity.
- Large groups create steric repulsion as the nucleophile approaches the α -carbon, dramatically slowing or even stopping the S_N2 reaction.



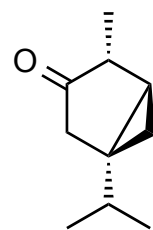
molecule is crowded near the nucleophilic atoms, so S_N2 reaction is slow

The Electrophile in S_N2 Reactions



- When considering the nature of the electrophile in S_N2 reactions, there are two factors to consider:
 1. The leaving group
 2. The substitution pattern at the α -carbon
- 1. The Leaving Group (LG)
 - The leaving group serves 2 main functions. First, it helps to polarize the carbon-LG bond, increasing the positive charge at the α -carbon making it more reactive towards nucleophiles.
 - Second, the leaving group leaves ***with a pair of electrons***. Good leaving groups are weak bases.

The Electrophile in S_N2 Reactions



- The halogens are commonly used leaving groups because the halides (except F⁻) are weak bases.



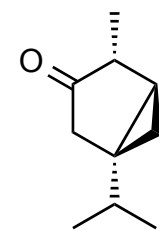
- The OH⁻ and OR⁻ group is a very poor leaving group because they are strong bases.



reaction cannot proceed because OH[⊖] is a very poor leaving group (strong base)

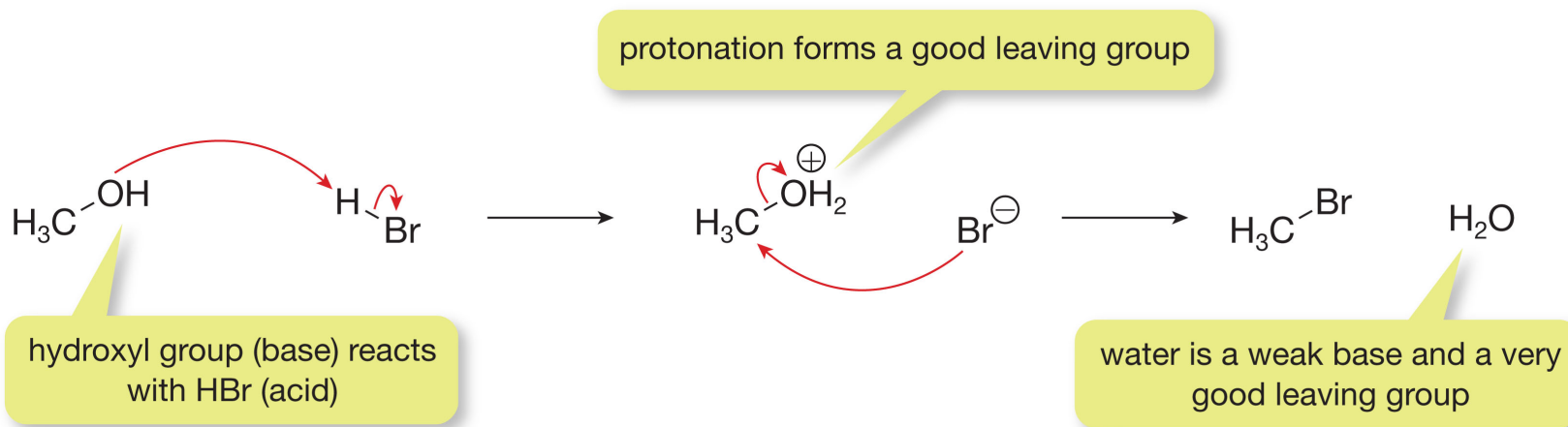
- Fortunately, these groups can be converted into good leaving groups by chemical modification.

The Electrophile in S_N2 Reactions

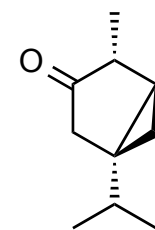


Acid Catalysis:

- One strategy is to use a strong acid to protonate the OH (or OR) group and convert it to an OH_2^+ (or ORH^+) group. This is a very good LG, as H_2O (or ROH) is a weak base.



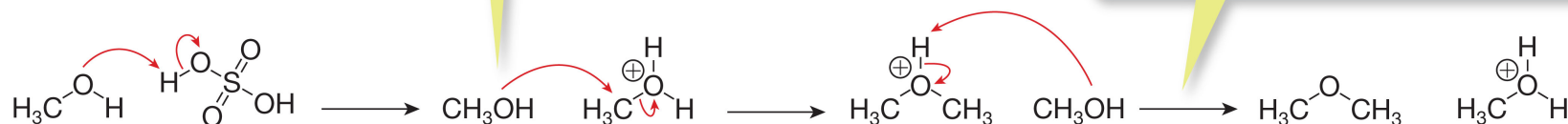
The Electrophile in S_N2 Reactions



Acid Catalysis:

- Strong acids such as HCl, HBr, and HI are used when the halide is used as the nucleophile.
- If another nucleophile is needed, strong acids such as H_2SO_4 and H_3PO_4 are used as their counterions are non-nucleophilic.

When acid is used, the nucleophile must be in its neutral form, as its conjugate base will not exist in an acidic solution.

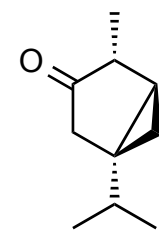


acid-base step generates neutral product

electrophile is activated by acid in the first step

nucleophile can react in its neutral form

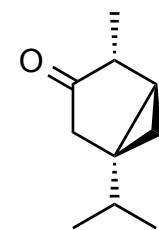
The Electrophile in S_N2 Reactions



Acid Catalysis:

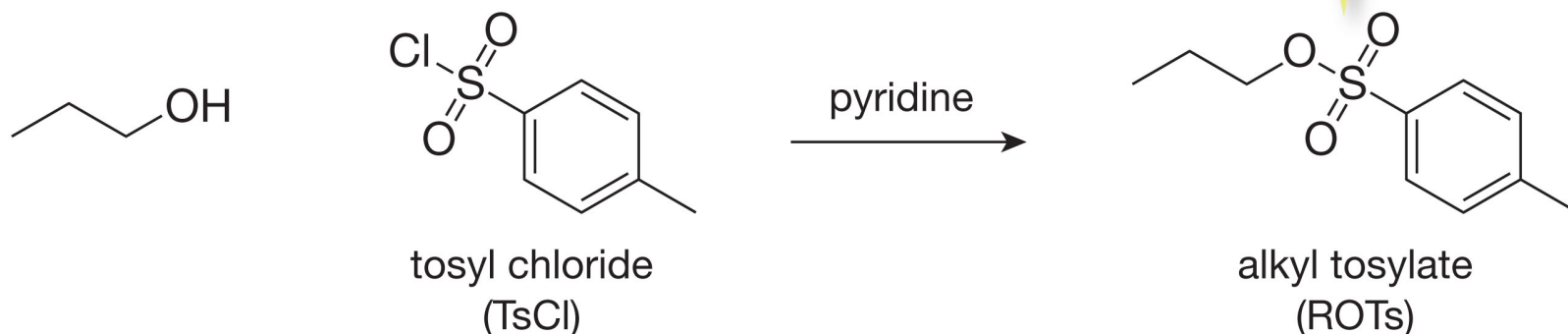
- A general principle in catalysis in chemical reactions is that a base accelerates reactions by activating the nucleophile, whereas an acid accelerates reactions by activating the electrophile.
 - A base converts a neutral nucleophile into a (-) charged conjugate base that is better able to donate its electrons.
 - An acid converts a neutral electrophile into a (+) charged conjugate acid that is better able to accept electrons.

The Electrophile in S_N2 Reactions

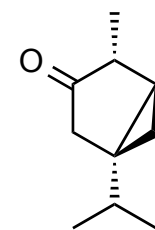


Sulfonate Esters:

- Another method in converting OH groups into better leaving groups is to convert it to a sulfonate ester (does not work for OR groups).

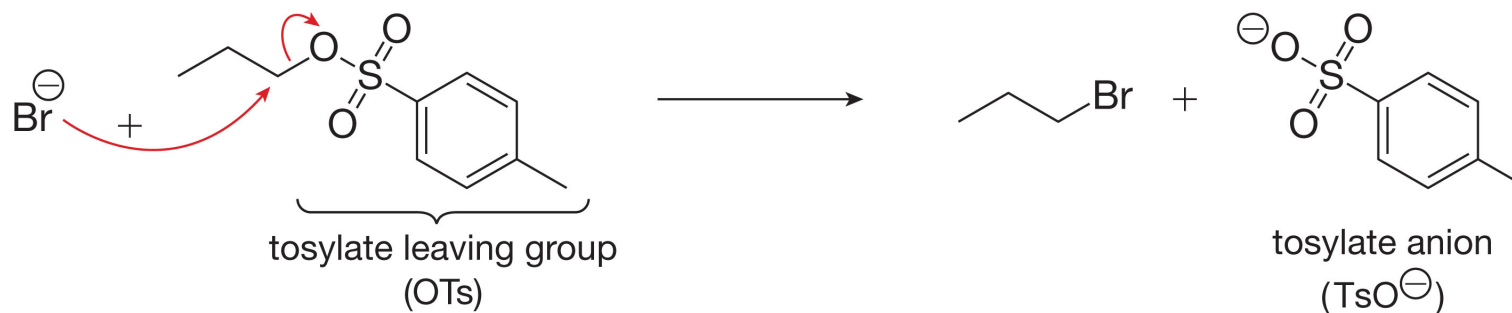


The Electrophile in S_N2 Reactions

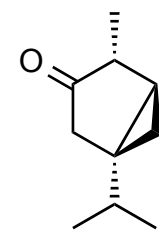


Sulfonate Esters:

- Sulfonate esters are good leaving groups because the leaving group, a sulfonate anion, is a weak base.

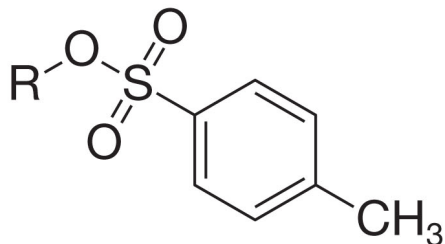


The Electrophile in S_N2 Reactions

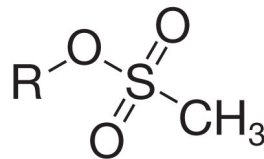


Sulfonate Esters:

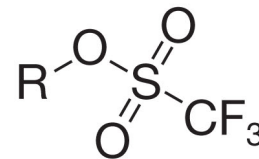
- Of the many sulfonate esters available, the following three are the most common:



tosylate (OTs)
(*p*-toluenesulfonate)

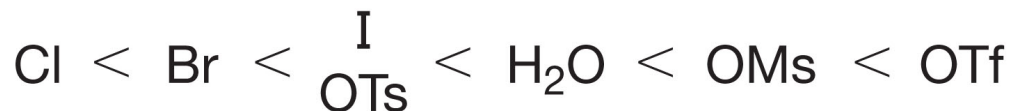


mesylate (OMs)
(methanesulfonate)



triflate (OTf)
(trifluoromethanesulfonate)

approximate order of leaving group ability

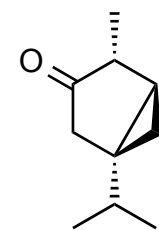


good

better

best

The Electrophile in S_N2 Reactions

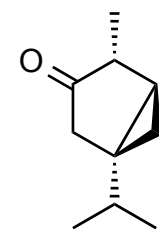


2. The substitution pattern at the α -carbon

- Steric hindrance around the α -carbon can influence the mechanism of displacement reactions.
 - Methyl and primary alkyl halides undergo S_N2 reactions very quickly.
 - Secondary substrates under S_N2 reactions more slowly.
 - Tertiary substrates do not react by S_N2 mechanisms.

Compound	α -Carbon structure	Symbol	Relative speed of S _N 2
CH ₃ Br	methyl	Me	fast
CH ₃ CH ₂ Br	primary	1°	↓
(CH ₃) ₂ CHBr	secondary	2°	slow
(CH ₃) ₃ CBr	tertiary	3°	does not undergo S _N 2

The Electrophile in S_N2 Reactions



2. The substitution pattern at the α -carbon

- Can we rationalize the following data?

Substrate	Relative Rate of S_N2 Reaction
CH_3Br	1.00
$\text{CH}_3\text{CH}_2\text{Br}$	1.31
$\text{CH}_3\text{CH}_2\text{CH}_2\text{Br}$	0.81
$(\text{CH}_3)_2\text{CHCH}_2\text{Br}$	0.052
$(\text{CH}_3)_3\text{CCH}_2\text{Br}$	0.00001
$(\text{CH}_3)_3\text{CBr}$	0.004