Organic Reactions
# 2 - Substitution – $S_N{}^2$ and $S_N{}^1$

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Kinetics of Nucleophilic Reaction

- Rate law is order of reaction
- 0 order is when rate of reaction is unaffected by change in concentration of the reactants
- 1st order is when rate of reaction doubles when one of the reactants is doubled
- 2nd order is when rate of reaction quadruples when two of the reactants are doubled
- Order of reaction explains the reaction mechanism

Nucleophilic Substitution Reactions

- In this reaction a nucleophile is a species with an unshared electron pair which reacts with an electron deficient carbon
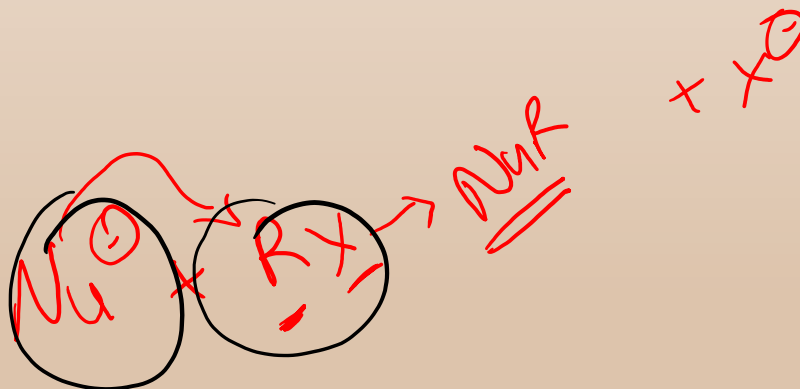
- A leaving group is substituted by a nucleophile
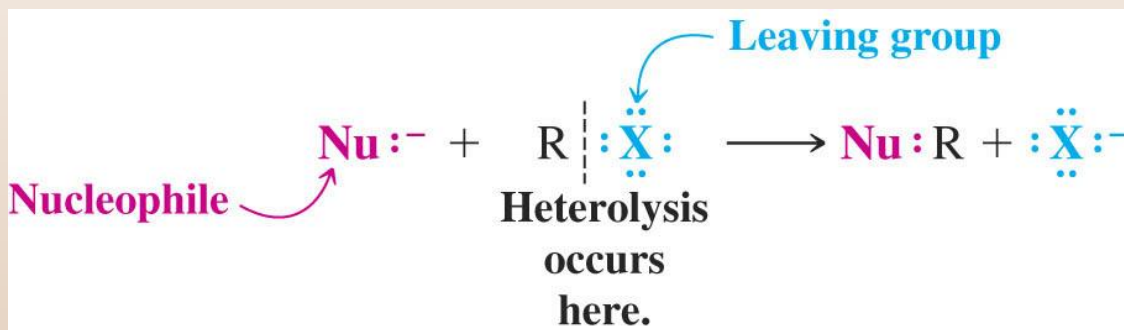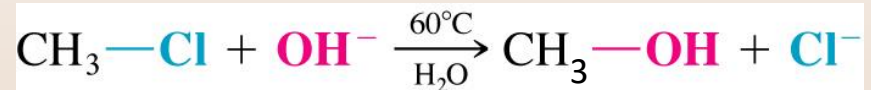

- Examples of nucleophilic substitution
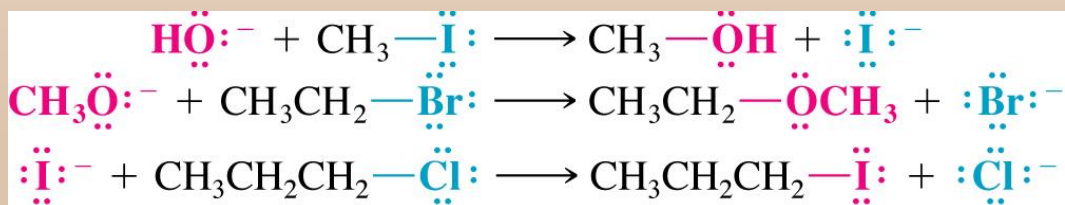
The S$_N$2 Reaction

- 2nd order substitution reaction
- S=substitution
- N (subscript) = nucleophilic
- 2 = (bimolecular) both nucleophile and substrate in rate determining step
- Inversion of stereochemistry occurs

$$Nu^- + RX \rightarrow NuR + X^-$$

An S$_N$2 Reaction

- The initial rate of the following reaction is measured

$$CH_3-Cl + OH^- \xrightarrow[H_2O]{60°C} CH_3-OH + Cl^-$$
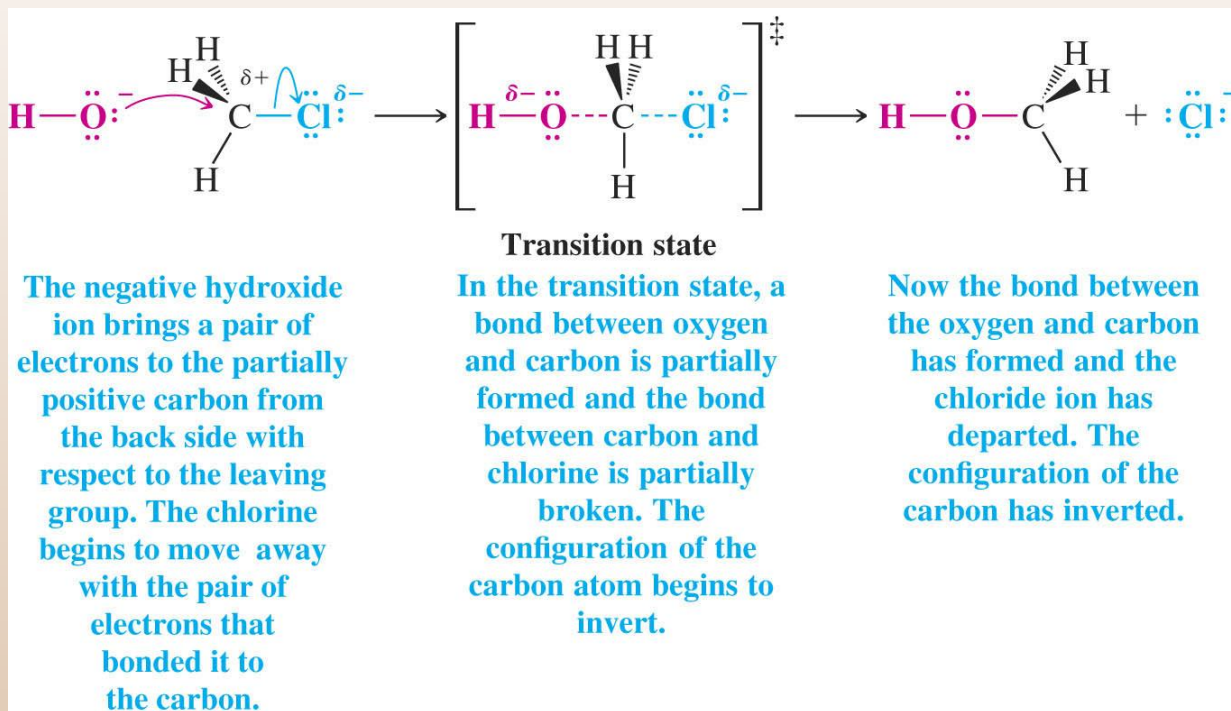
- The rate is directly proportional to the initial concentrations of both methyl chloride (substrate) and hydroxide (nucleophile)

| Experiment Number	Initial [CH$_3$Cl]	Initial [OH$^-$]	Initial Rate (mol L^{-1} s^{-1})
1	0.0010	1.0	4.9×10^{-7}
2	0.0020	1.0	9.8×10^{-7}
3	0.0010	2.0	9.8×10^{-7}
4	0.0020	2.0	19.6×10^{-7}

$$\text{Rate} = k[CH_3Cl][OH^-]$$

- The rate equation reflects this dependence
- S$_N$2 reaction: substitution, nucleophilic, 2nd order (bimolecular)

A Mechanism for the S$_N$2 Reaction

Transition state

The negative hydroxide ion brings a pair of electrons to the partially positive carbon from the back side with respect to the leaving group. The chlorine begins to move away with the pair of electrons that bonded it to the carbon.

In the transition state, a bond between oxygen and carbon is partially formed and the bond between carbon and chlorine is partially broken. The configuration of the carbon atom begins to invert.

Now the bond between the oxygen and carbon has formed and the chloride ion has departed. The configuration of the carbon has inverted.

– A *transition state* is the high energy state of the reaction
  • It is an unstable entity with a very brief existence (10^{-12} s)
– In the transition state of this reaction bonds are partially formed and broken
    – Both chloromethane and hydroxide are involved in the transition state and this explains why the reaction is second order
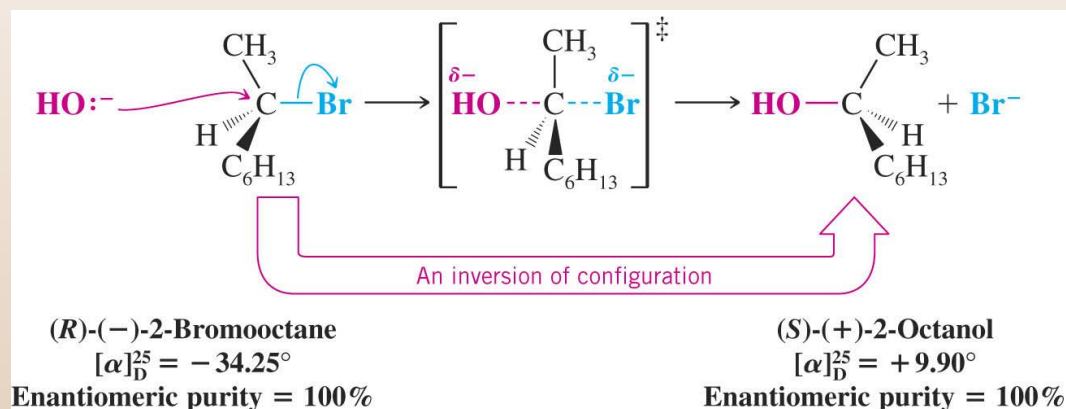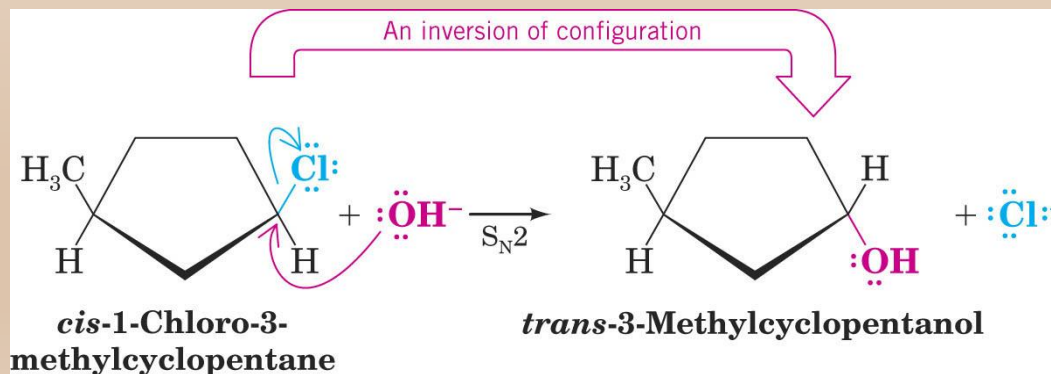
S$_N$2 Energy Diagram
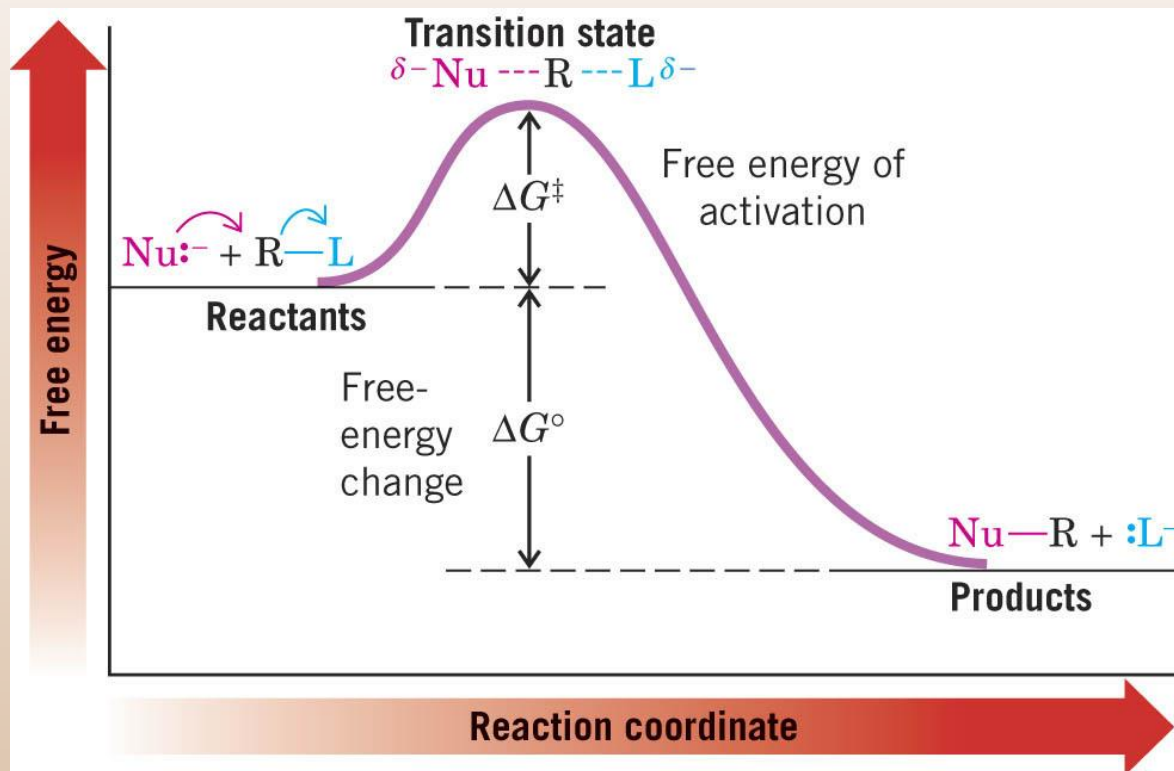
- One-step reaction.
- Transition state is highest in energy.

The Stereochemistry of S$_N$2 Reactions

- Backside attack of nucleophile results in an inversion of configuration


(R)-(−)-2-Bromooctane
$[\alpha]_D^{25} = -34.25°$
Enantiomeric purity = 100%

(S)-(+)-2-Octanol
$[\alpha]_D^{25} = +9.90°$
Enantiomeric purity = 100%

- In cyclic systems a cis compound can react and become trans product

cis-1-Chloro-3-methylcyclopentane
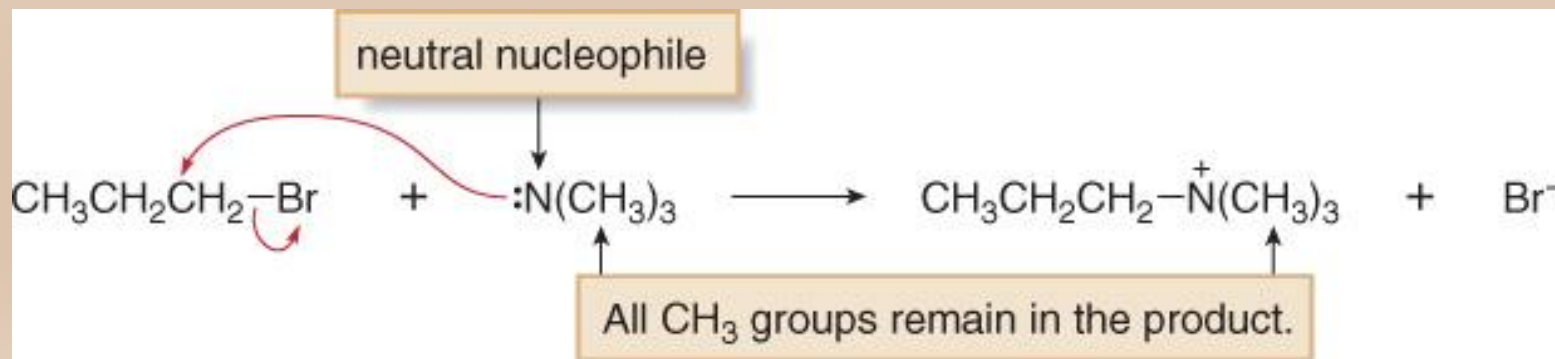
trans-3-Methylcyclopentanol

Examples of Nucleophilic Substitution

- Negatively charged nucleophiles like HO^- and HS^- are used as salts with Li^+, Na^+, or K^+ counterions to balance the charge. Since the identity of the counterion is usually inconsequential, it is often omitted from the chemical equation.

$CH_3CH_2CH_2-Br$ + Na^+ :$\ddot{O}H^-$ $\longrightarrow$ $CH_3CH_2CH_2-\ddot{O}H$ + Na^+Br^-

Na$^+$ balances charge.
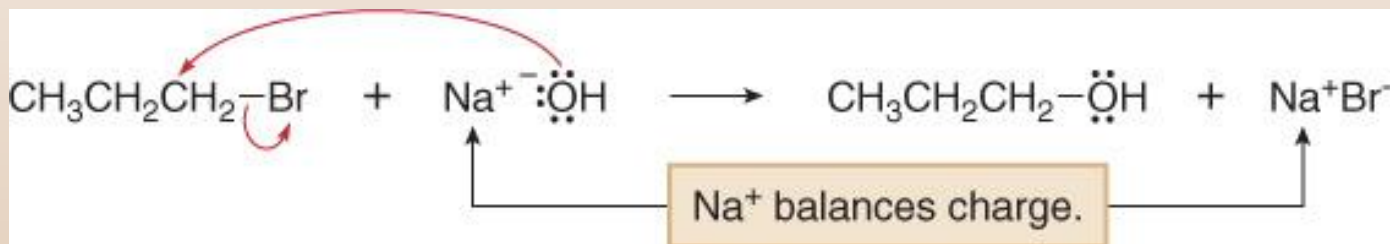
- When a neutral nucleophile is used, the substitution product bears a positive charge.

neutral nucleophile

$CH_3CH_2CH_2-Br$ +   :$N(CH_3)_3$ $\longrightarrow$ $CH_3CH_2CH_2-\overset{+}{N}(CH_3)_3$ + Br^-

All CH$_3$ groups remain in the product.

Uses for S$_N$2 Reactions

- Synthesis of other classes of compounds.
- Halogen exchange reaction.

$$Nuc:^- \quad + \quad R-X \quad \longrightarrow \quad Nuc-R \quad + \quad X^-$$

Nucleophile		Product	Class of Product
$R-X \ + \ ^-:\ddot{\underset{..}{I}}:$	$\longrightarrow$	$R-\ddot{\underset{..}{I}}:$	alkyl halide
$R-X \ + \ ^-:\ddot{\underset{..}{O}}H$	$\longrightarrow$	$R-\ddot{\underset{..}{O}}H$	alcohol
$R-X \ + \ ^-:\ddot{\underset{..}{O}}R'$	$\longrightarrow$	$R-\ddot{\underset{..}{O}}R'$	ether
$R-X \ + \ ^-:\ddot{\underset{..}{S}}H$	$\longrightarrow$	$R-\ddot{\underset{..}{S}}H$	thiol (mercaptan)
$R-X \ + \ ^-:\ddot{\underset{..}{S}}R'$	$\longrightarrow$	$R-\ddot{\underset{..}{S}}R'$	thioether (sulfide)
$R-X \ + \ :NH_3$	$\longrightarrow$	$R-NH_3^+ \ X^-$	amine
$R-X \ + \ ^-:\ddot{N}=\overset{+}{N}=\ddot{N}:^-$	$\longrightarrow$	$R-\ddot{N}=\overset{+}{N}=\ddot{N}:^-$	azide
$R-X \ + \ ^-:C\equiv C-R'$	$\longrightarrow$	$R-C\equiv C-R'$	alkyne
$R-X \ + \ ^-:C\equiv N:$	$\longrightarrow$	$R-C\equiv N:$	nitrile
$R-X \ + \ R'-C\ddot{\underset{..}{O}}O:^-$	$\longrightarrow$	$R'-COO-R$	ester
$R-X \ + \ :P(Ph)_3$	$\longrightarrow$	$[R-PPh_3]^+ \ ^-X$	phosphonium salt

S$_N$1 Reaction

- Unimolecular nucleophilic substitution.

- Two step reaction with carbocation intermediate.

- Rate is first order in the alkyl halide, zero order in the nucleophile.
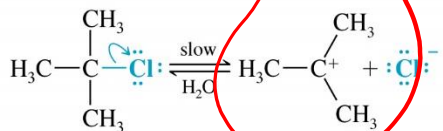
- Racemization occurs.
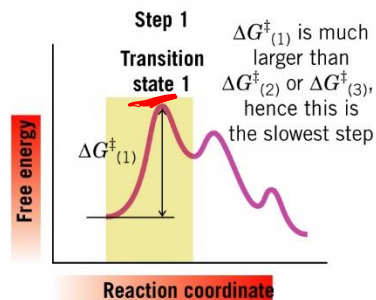
The S$_N$1 Reaction Mechanism

$$(CH_3)_3CCl + 2\ H_2O \longrightarrow (CH_3)_3COH + H_3O^+ + Cl^-$$

Mechanism:

Step 1

H$_3$C—C(—CH$_3$)(—CH$_3$)—Cl: $\xrightarrow[H_2O]{\text{slow}}$ H$_3$C—C$^+$(—CH$_3$)(—CH$_3$) + :Cl:$^-$
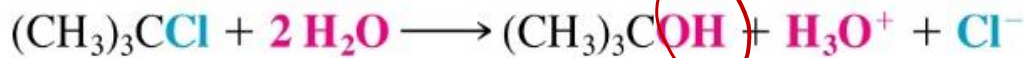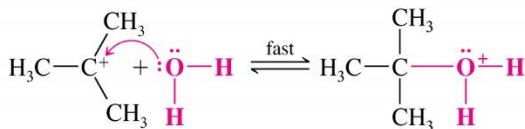
Aided by the polar solvent a chlorine departs with the electron pair that bonded it to the carbon.

This slow step produces the relatively stable 3Y carbocation and a chloride ion. Although not shown here, the ions are solvated (and stabilized) by water molecules.
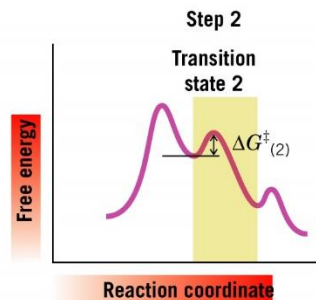
Step 1
Transition state 1

$\Delta G^{\ddagger}_{(1)}$ is much larger than $\Delta G^{\ddagger}_{(2)}$ or $\Delta G^{\ddagger}_{(3)}$, hence this is the slowest step

Free energy — $\Delta G^{\ddagger}_{(1)}$

Reaction coordinate

Step 2

H$_3$C—C$^+$(—CH$_3$)(—CH$_3$) + :Ö—H(H) $\xrightarrow{\text{fast}}$ H$_3$C—C(—CH$_3$)(—CH$_3$)—Ö$^+$—H(H)
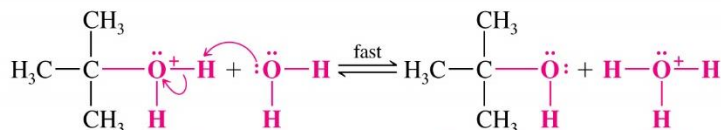
A water molecule acting as a Lewis base donates an electron pair to the carbocation (a Lewis acid). This gives the cationic carbon eight electrons.

The product is a *tert*-butyloxonium ion (or protonated *tert*-butyl alcohol).

Step 2
Transition state 2

Free energy — $\Delta G^{\ddagger}_{(2)}$

Reaction coordinate

Step 3

H$_3$C—C(—CH$_3$)(—CH$_3$)—Ö$^+$—H(H) + :Ö—H(H) $\xrightarrow{\text{fast}}$ H$_3$C—C(—CH$_3$)(—CH$_3$)—Ö: + H—Ö$^+$—H(H)

A water molecule acting as a Brønsted base accepts a proton from the *tert*-butyloxonium ion.

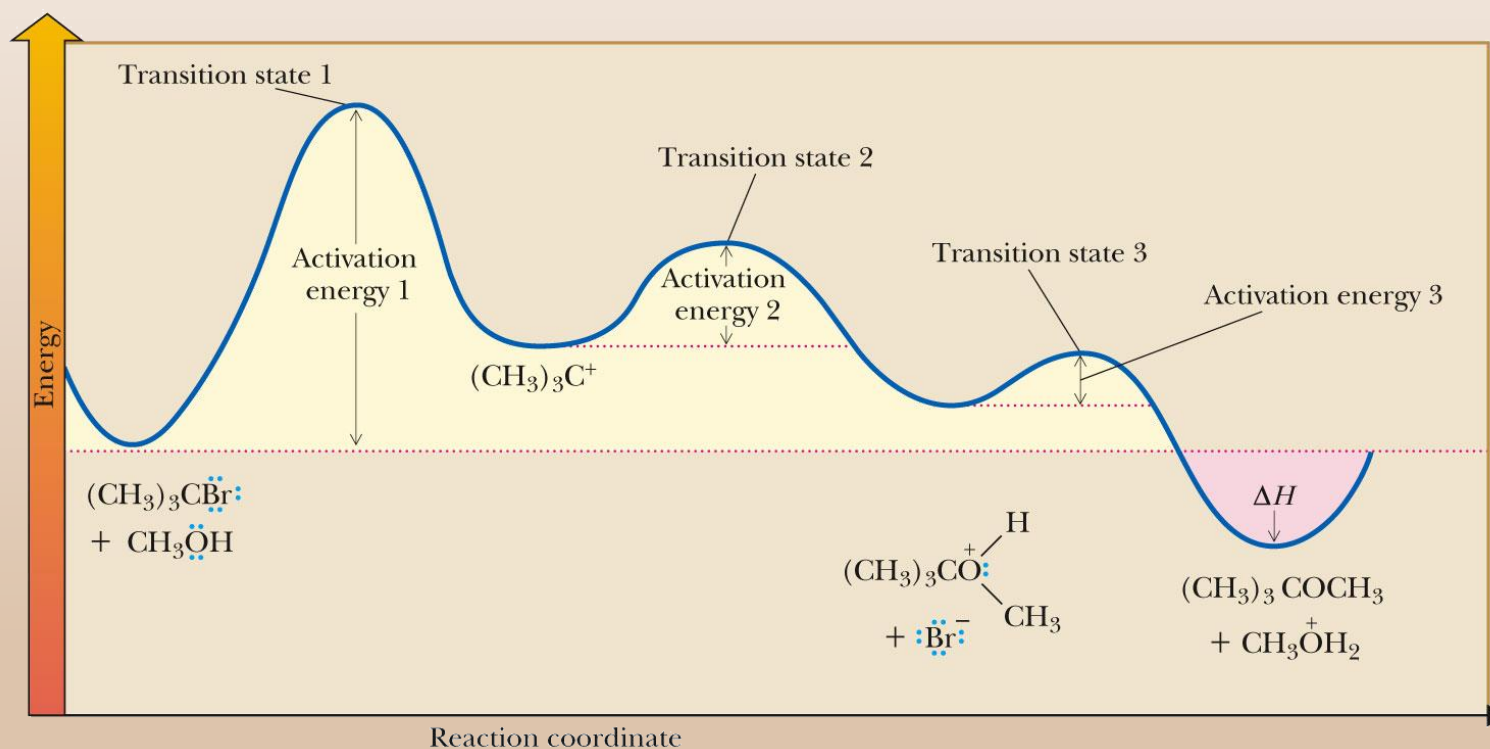The products are *tert*-butyl alcohol and a hydronium ion.

Step 3
Transition state 3

Free energy — ΔH — $\Delta G^{\ddagger}_{(3)}$

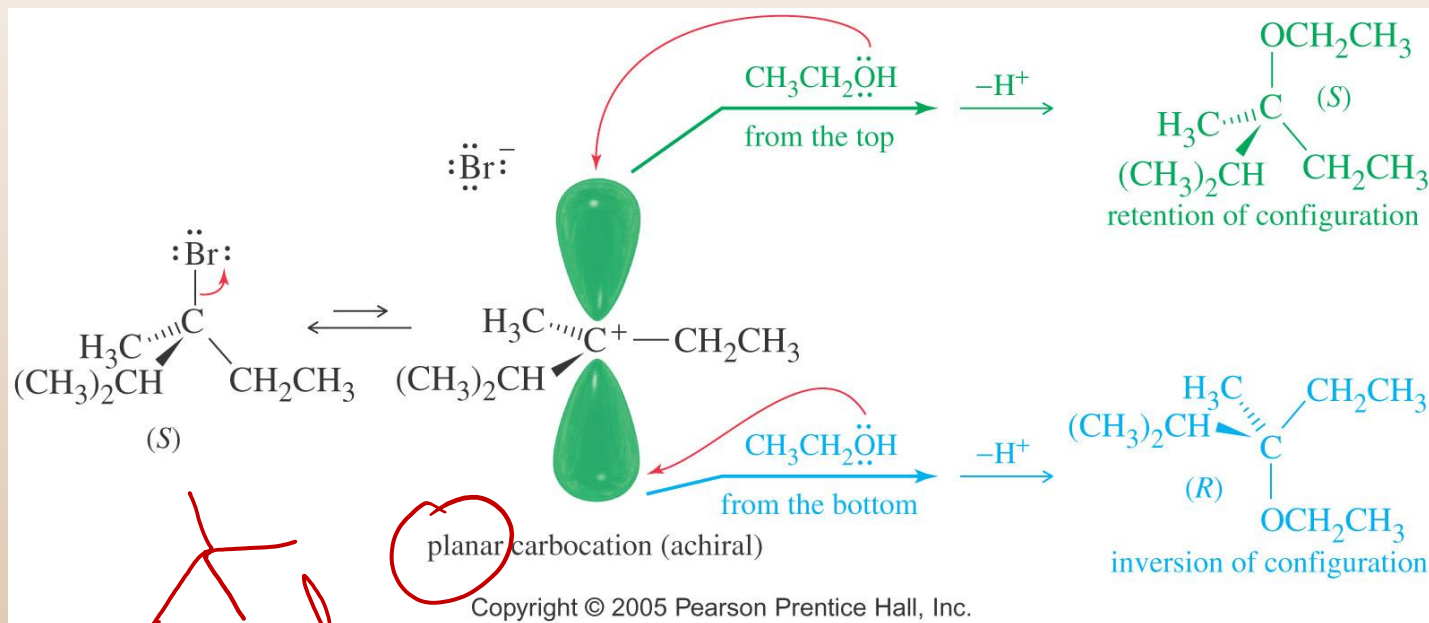**Reaction coordinate**

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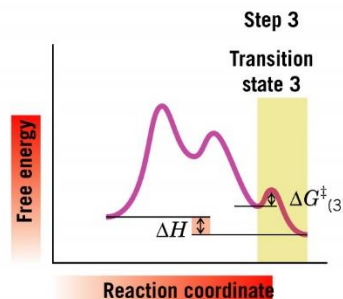
S$_N$1 Energy Diagram

- There are three transition states. Step1 crosses the highest energy barrier and is rate determining

Stereochemistry of S$_N$1

Racemization: inversion <u>and</u> retention

Key Words/Concepts

- Substitution Reaction
- Nucleophile
- Electrophile
- Leaving group
- 1st order reaction (unimolecular)
- 2nd order reaction (bimolecular)
- Transition state
- Rate determining step
- Carbocation
- Configuration (inversion and retention)