

Module 3, Lecture 7

Structure and Reactions of Organic Molecules

**Introduction to reaction mechanisms
Substitution**

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References to Brown *et al* text shown in BLUE

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Learning Objectives:

- to have an understanding of “curved” arrow notation
- to have an understanding of nucleophilic substitution reactions
- to be able to identify and write an S_N1 reaction mechanism
- to have an understanding of the factors that lead to S_N1 or S_N2 reaction pathways

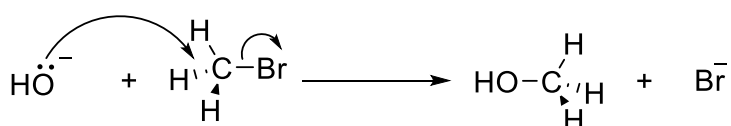
Textbook: Chapter 25, sections 25.4-25.5, Brown

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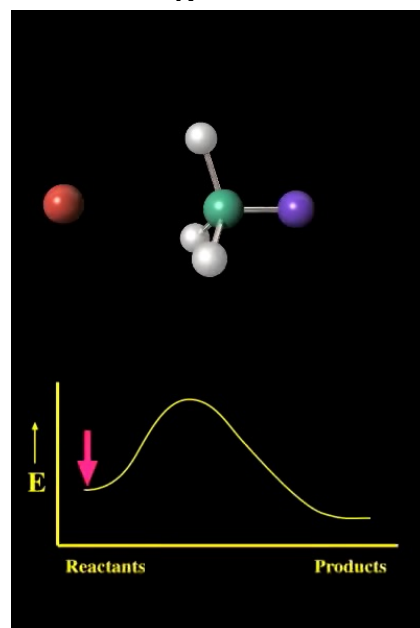
Nucleophilic Substitution - OPTION 1 S_N2

bromomethane + NaOH → methanol + NaBr

rate = $k [\text{CH}_3\text{Br}] [\text{HO}^-]$



Nucleophile OH^- approaches and attaches opposite to the leaving group Br^- .

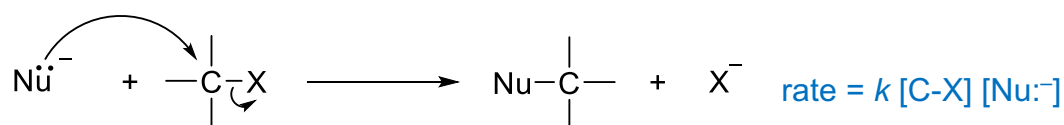


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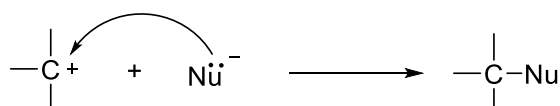
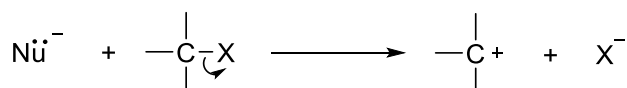
Nucleophilic Substitution

Possible Reaction Sequences for nucleophilic substitution:

- X^- leaves as Nu^- attaches: **OPTION 1**



- X^- leaves and then Nu^- attaches: **OPTION 2**



If 1st step is rate determining: $\text{rate} = k [\text{C-X}]$

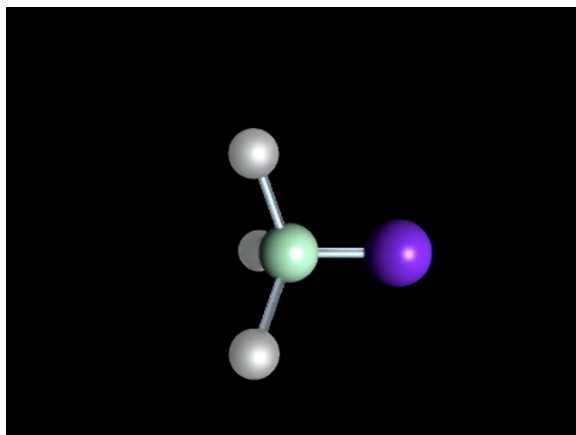
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Nucleophilic Substitution - OPTION 2

$$\text{rate} = k [\text{C-X}]$$

2 step reaction

X leaves in slow step followed by fast attachment of Nu^-



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Nucleophilic Substitution - OPTION 2

$$\text{rate} = k [\text{C-X}]$$

2 step reaction

X leaves in slow step followed by fast attachment of Nu^-

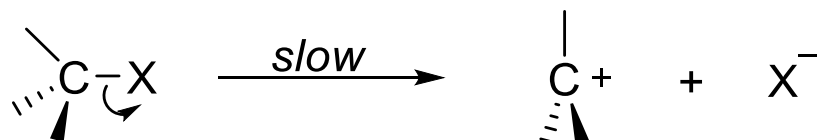
1st order reaction - mechanism is called **$\text{S}_{\text{N}}1$** (25.7)

Substitution Nucleophilic 1st order

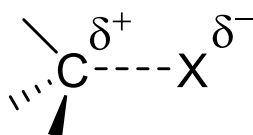
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Nucleophilic Substitution - OPTION 2 S_N1

Slow step - removal of leaving group:



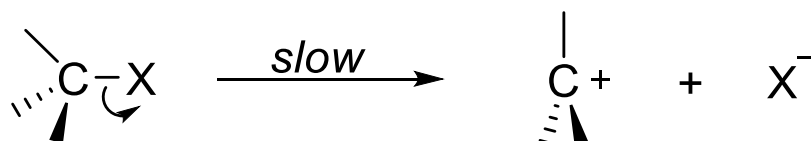
- Independent of nucleophile
- Bond stretched to breaking point - transition state:



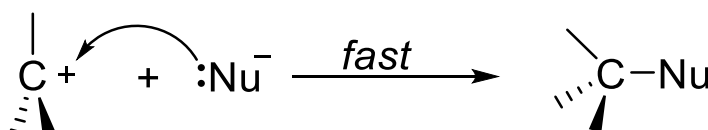
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Nucleophilic Substitution - OPTION 2 S_N1

Slow step - removal of leaving group:



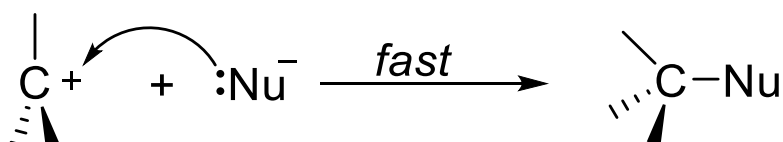
Fast step – addition of the nucleophile:



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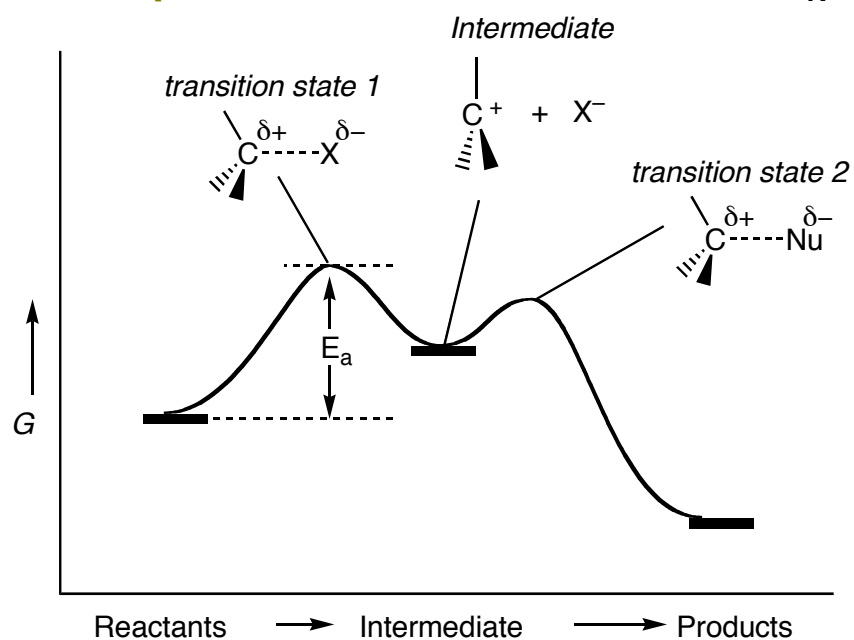
Nucleophilic Substitution - OPTION 2 S_N1

- Carbocation has a definite lifetime
- **reaction intermediate** (25.7)
- Very reactive - reacts with *any* nucleophile it collides with
- Major product from reaction with most *abundant* nucleophile



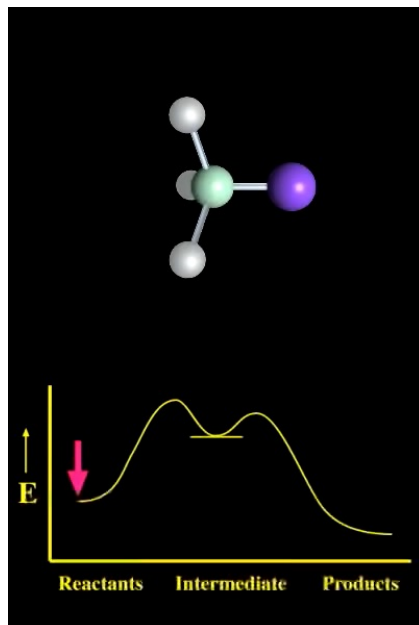
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Nucleophilic Substitution - OPTION 2 S_N1



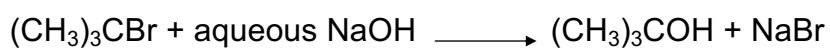
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Nucleophilic Substitution - OPTION 2 S_N1

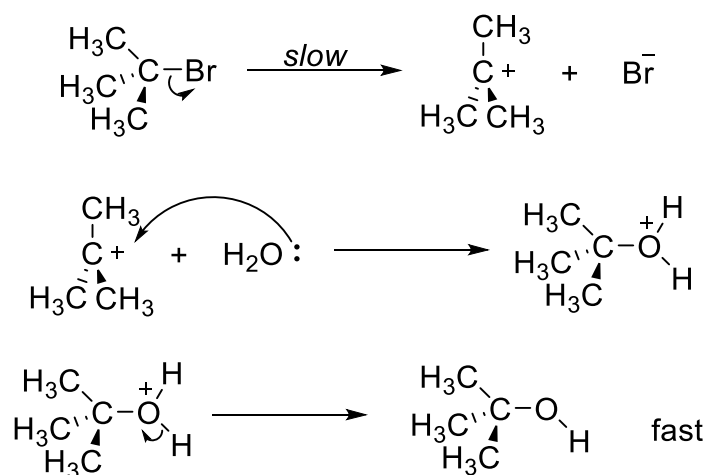


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S_N1 Example



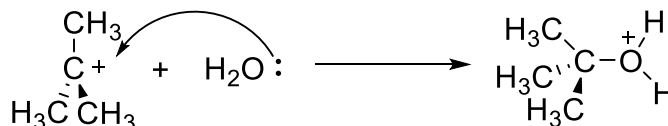
$$\text{rate} = k [(\text{CH}_3)_3\text{CBr}]$$



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Nucleophilic Substitution - OPTION 2 S_N1

The most abundant nucleophile in the system is H₂O:



Note:

- Nucleophile is neutral (not charged)
- Product has +ve charge on O

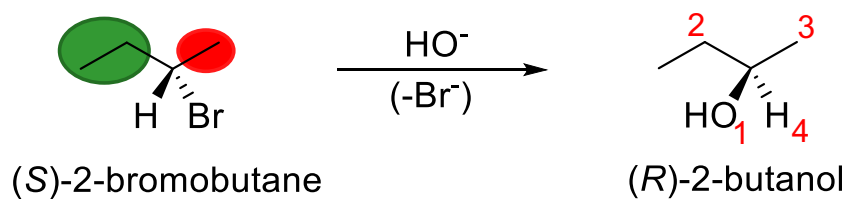
Lose H⁺ (deprotonate) to complete reaction - an extra step

What would the energy profile of this reaction look like?

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Stereochemistry of S_N1 and S_N2 reactions

Can be used to distinguish between an S_N1 and an S_N2 mechanism.

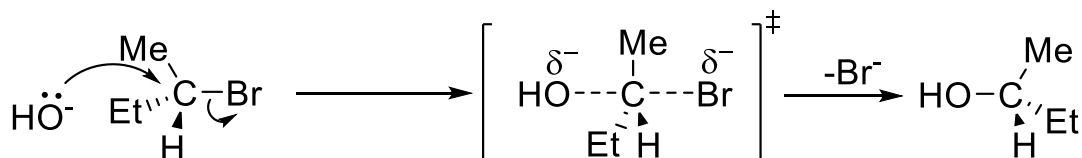


Inversion of configuration

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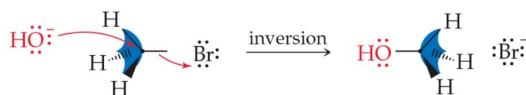
Stereochemistry of S_N1 and S_N2 reactions

Rationalised by the S_N2 mechanism: OH⁻ approaches opposite to the leaving group Br⁻



S_N2 reaction is stereospecific.

Product from reaction with the (*R*)-bromide???

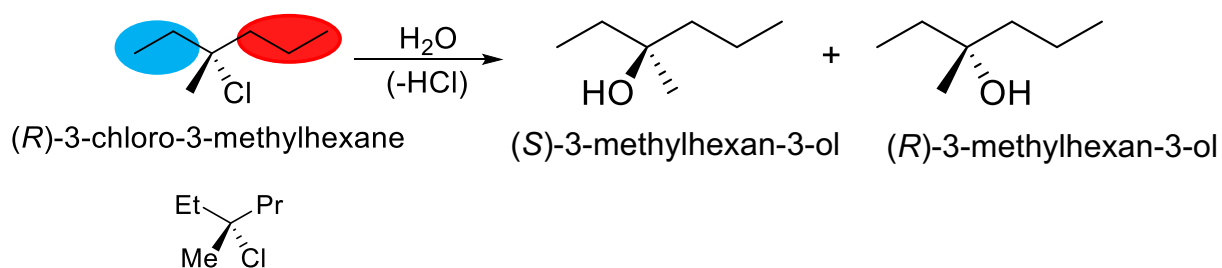


► FIGURE 25.17 The mechanism of an S_N2 reaction is analogous to an umbrella on a windy day.



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Stereochemistry of S_N1 and S_N2 reactions



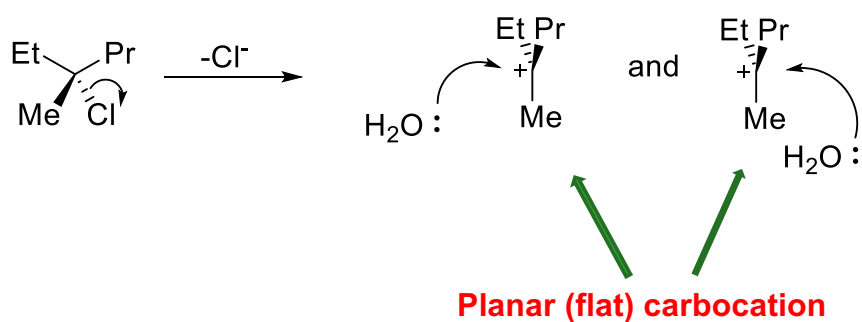
Reaction occurs with inversion **and** retention of configuration.

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Stereochemistry of S_N1 and S_N2 reactions

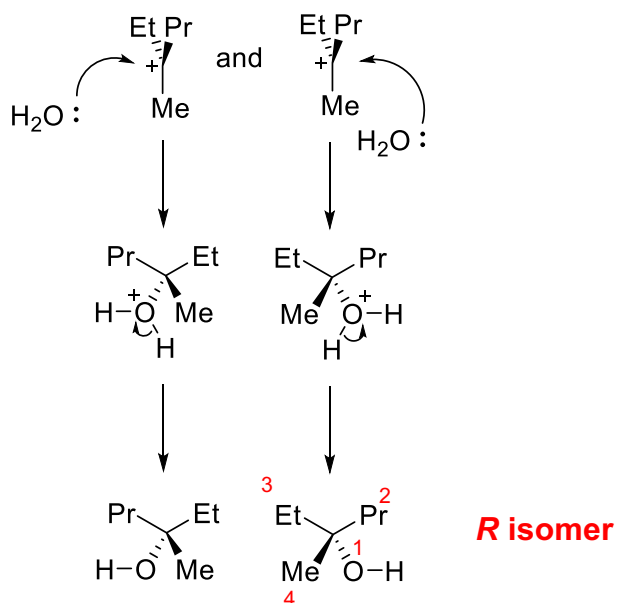
Rationalised by an S_N1 mechanism:

Nucleophile H₂O can approach and attach to a planar reaction intermediate (carbocation) from either side.



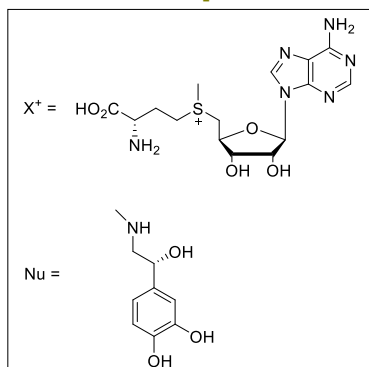
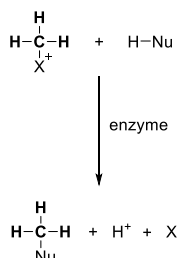
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Stereochemistry of S_N1 and S_N2 reactions

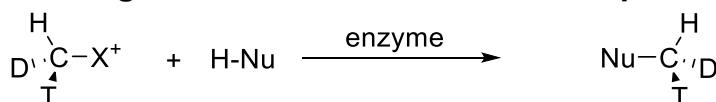


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Previous example



To determine the mechanism of this reaction an experiment was conducted using a chiral methyl group (**featuring the tritium and deuterium isotopes of hydrogen**).

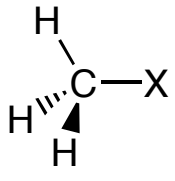
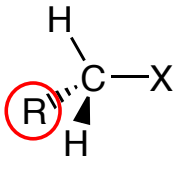
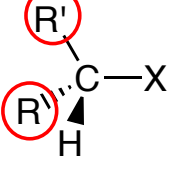
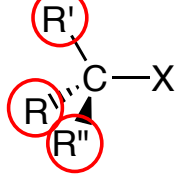


What is the mechanism of this nucleophilic substitution reaction?

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What determines whether a reaction goes via $\text{S}_{\text{N}}1$ or $\text{S}_{\text{N}}2$?

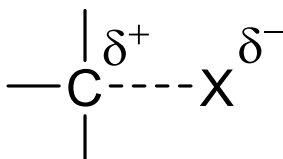
Experimental observations:

			
methyl	1° primary	2° secondary	3° tertiary
Usually $\text{S}_{\text{N}}2$	Usually $\text{S}_{\text{N}}2$	$\text{S}_{\text{N}}1$ or $\text{S}_{\text{N}}2$	Usually $\text{S}_{\text{N}}1$

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What determines whether a reaction goes via S_N1 or S_N2?

S_N1 is fast if charges in first transition state can be delocalized (*stabilized*)

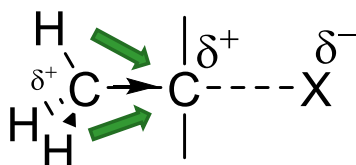


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What determines whether a reaction goes via S_N1 or S_N2?

S_N1 is fast if charges in first transition state can be delocalized (*stabilized*)

- Alkyl groups e donating (see 17.1, 706)
- Diminishes charge on central C

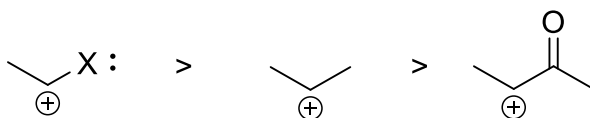


Effect increases with no. of alkyl groups - rate of S_N1 reaction increases:
methyl < 1° < 2° < 3

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Not all carbocations are equal

- Lone pairs stabilize adjacent carbocations, electron withdrawing groups destabilize adjacent carbocations :



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What determines whether a reaction goes via S_N1 or S_N2 ?

eg.



Alkyl halide	Type	Relative Rate
CH_3Br	methyl	1
$\text{CH}_3\text{CH}_2\text{Br}$	1°	1
$(\text{CH}_3)_2\text{CHBr}$	2°	12
$(\text{CH}_3)_3\text{CBr}$	3°	1.2×10^6

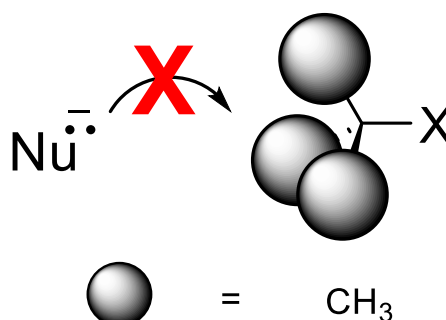
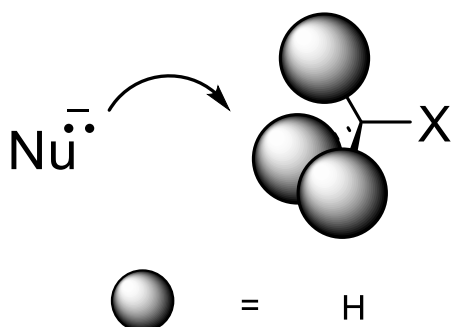
Increasing delocalization and stabilization of TS

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What determines whether a reaction goes via S_N1 or S_N2?

S_N2 is fast if approach of nucleophile is not sterically hindered

- Nu:⁻ collides with C atom from side opposite to leaving group
- Easy if groups attached to C are small (methyl or 1°)



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What determines whether a reaction goes via S_N1 or S_N2?



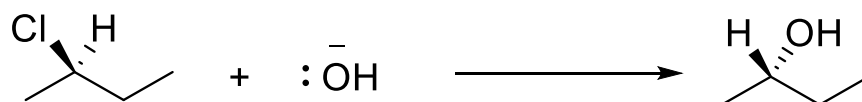
Alkyl Bromide (RBr)	Type	Relative Rate
CH ₃ Br	methyl	4 x 10 ³
CH ₃ CH ₂ Br	1°	80
(CH ₃) ₂ CHBr	2°	1
(CH ₃) ₃ CBr	3°	~0

Decreasing steric hindrance to attack at C

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Question

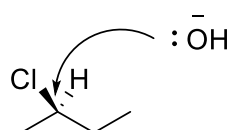
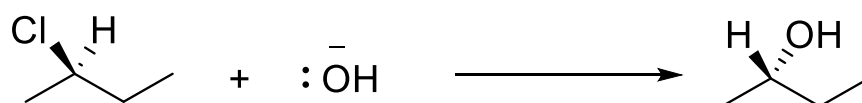
Provide a reaction mechanism for the following reaction.



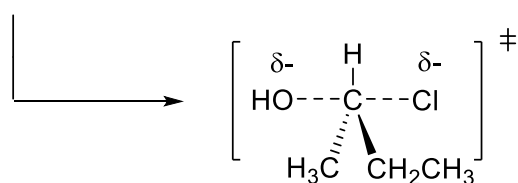
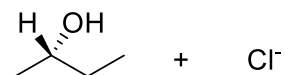
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Question

Provide a reaction mechanism for the following reaction.



Inversion of configuration



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

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*** Homework ***

Chemistry – the central science 15th Ed

Brown et al.

Problems 27.31, 27.73, 27.88 (a)

Answers on Blackboard