Objective 9

Apply Reactivity Principles to Substitution Reactions:
identify structural features (alpha C, LG)
Use curved arrows to predict product.
Compare S_N1 vs. S_N2 mechanisms.

4 Types of Organic Polar Reactions

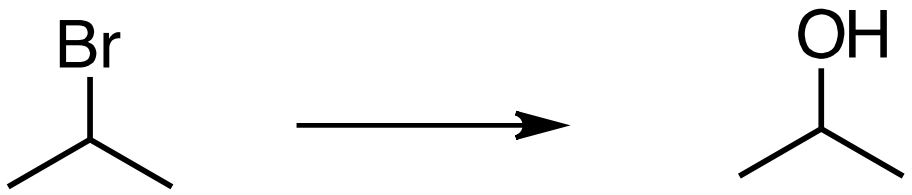
Acid-Base

Addition

Substitution

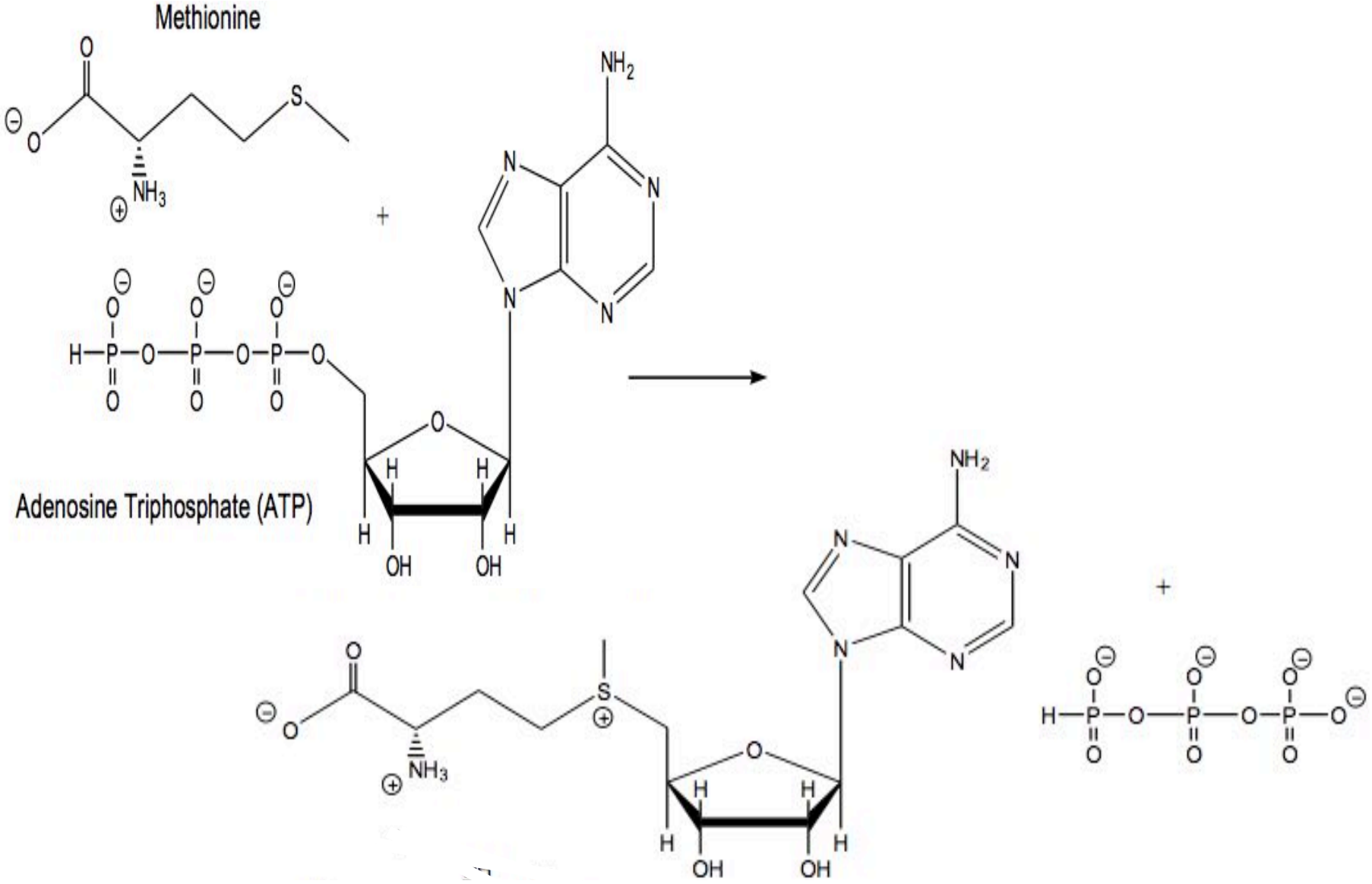
Elimination

Substitution Reaction: Exchange (substitute) one atom or group for another on the same carbon



Synthesis: a good way to convert one functional group to another

Substitution Reaction: Exchange (substitute) one atom or group for another on the same carbon

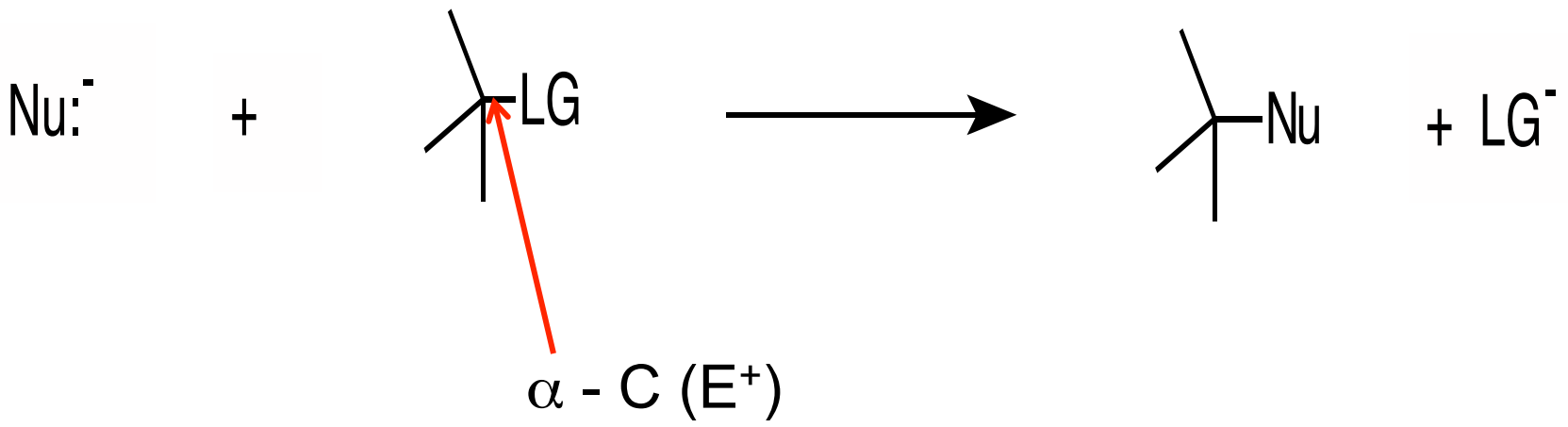


Structural Features *for* ***Substitution Reactions***

Need a:

1. Nucleophile ($Nu:^-$)
2. Electrophile (E^+) = Alpha (α) C = Carbon bonded to Leaving Group
3. Leaving Group = a base. See pK_a table.

The **Nucleophile Substitutes for the Leaving Group**:



A Leaving Group (LG) is a base. See pK_a table.

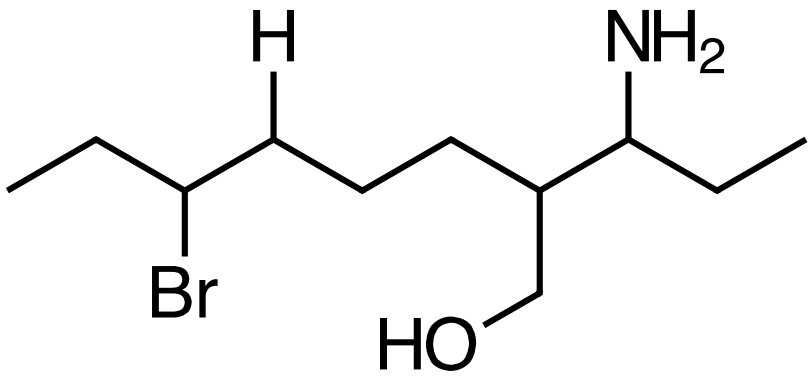
Which atom or group is a Leaving Group?

a. H
b. OH
c. Cl
d. $OOCCH_3$
e. $HOOCCH_3$
f. CH_3
g. NH_3

A Leaving Group (LG) is a base. See pK_a table.

Leaving Groups. Circle the Leaving Group(s).

a. ~~H~~
b. OH
c. Cl
d. $OOCCH_3$
e. ~~$HOOCCH_3$~~
f. ~~CH_3~~
g. NH_3



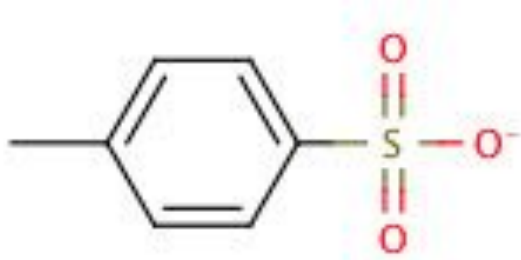
A Leaving Group (LG) is a base. See pK_a table.
A Good LG is a weak base.

Which LG is the best? Which LG is the worst?

a. Cl
b. Br
c. OH
d. H_2O

Leaving Groups, Carey, "Organic Chemistry", 8th ed., p. 348, Table 8.9

Excellent	TsO^-, NH_3
Very Good	I^-, H_2O
Good	Br^-
Fair	Cl^-
Poor	F^-
Very Poor	OH^-, NH_2^-, RO^-



Tosylate = TsO^-

Best LG are weak bases.

How does a LG affect reaction rate?

Which Leaving Group favors S_N1?
Which Leaving Group favors S_N2?

A Nucleophile (Nu:$^-$) is a base. See pK_a table.

Which atom or group is a Nucleophile?

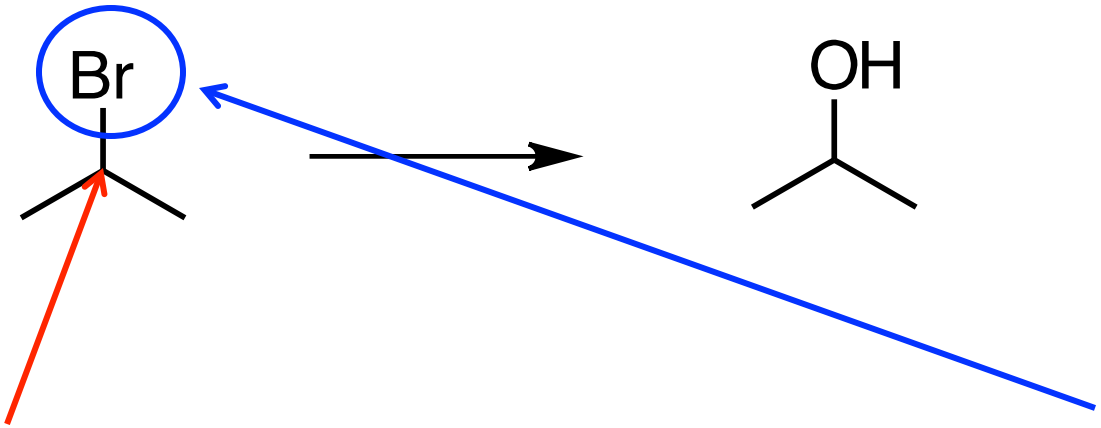
a. HBr
b. CH_3COO^-
c. Br^-
d. OH^-
e. H_2O
f. CH_3NH_2
g. NH_4^+

Nucleophile Strength, Carey, "Organic Chemistry", 8th ed., p. 333, Table 8.4

Reactivity Class	Nucleophile	Reactivity
Very Good	I^-, HS^-, RS^-	$> 10^5$
Good	Br^-, OH^-, RO^-, CN^-, N_3^-	10^4
Fair	NH_3, Cl^-, F^-, RCO_2^-	10^3
Weak	H_2O, ROH	1
Very Weak	RCO_2H	10^{-2}

Nu:$^-$ strength matches Base strength *except* for I^-, Br^-, Cl^-, F^-.

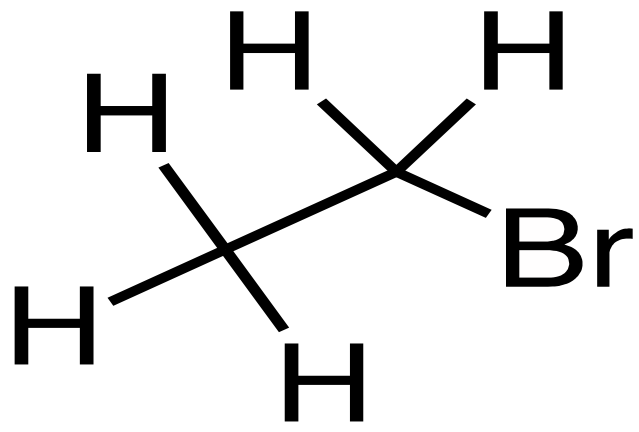
Substitution Reaction: Exchange (substitute) one atom or group for another on the same carbon



ID the alpha C.

What is the leaving group?

What nucleophile would you use in this reaction?
Use curved arrows to show how products form.



C-Br bond is polar because _____.

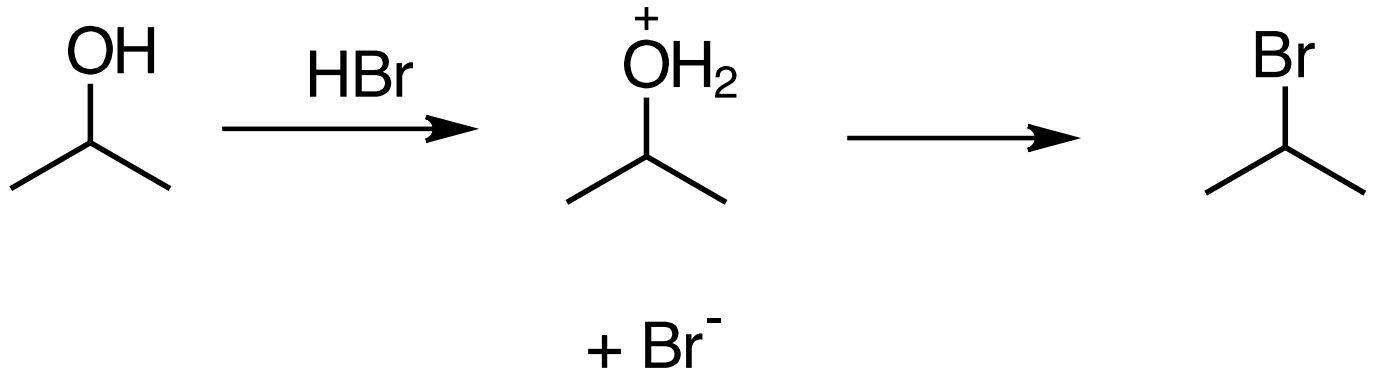
This C has a partial positive charge (δ+) because _____.

The alpha C is a _____.

a. nucleophile b. electrophile

c. neither d. both

Substitution Reaction: Exchange (substitute) one atom or group for another on the same carbon



ID the alpha C.
What is the leaving group? Is it a good LG?
(Why do you have to use HBr in the 1st step?)
What is the nucleophile?
Use curved arrows to show how products form.

Good LG = weak base. Poor LG = strong base.

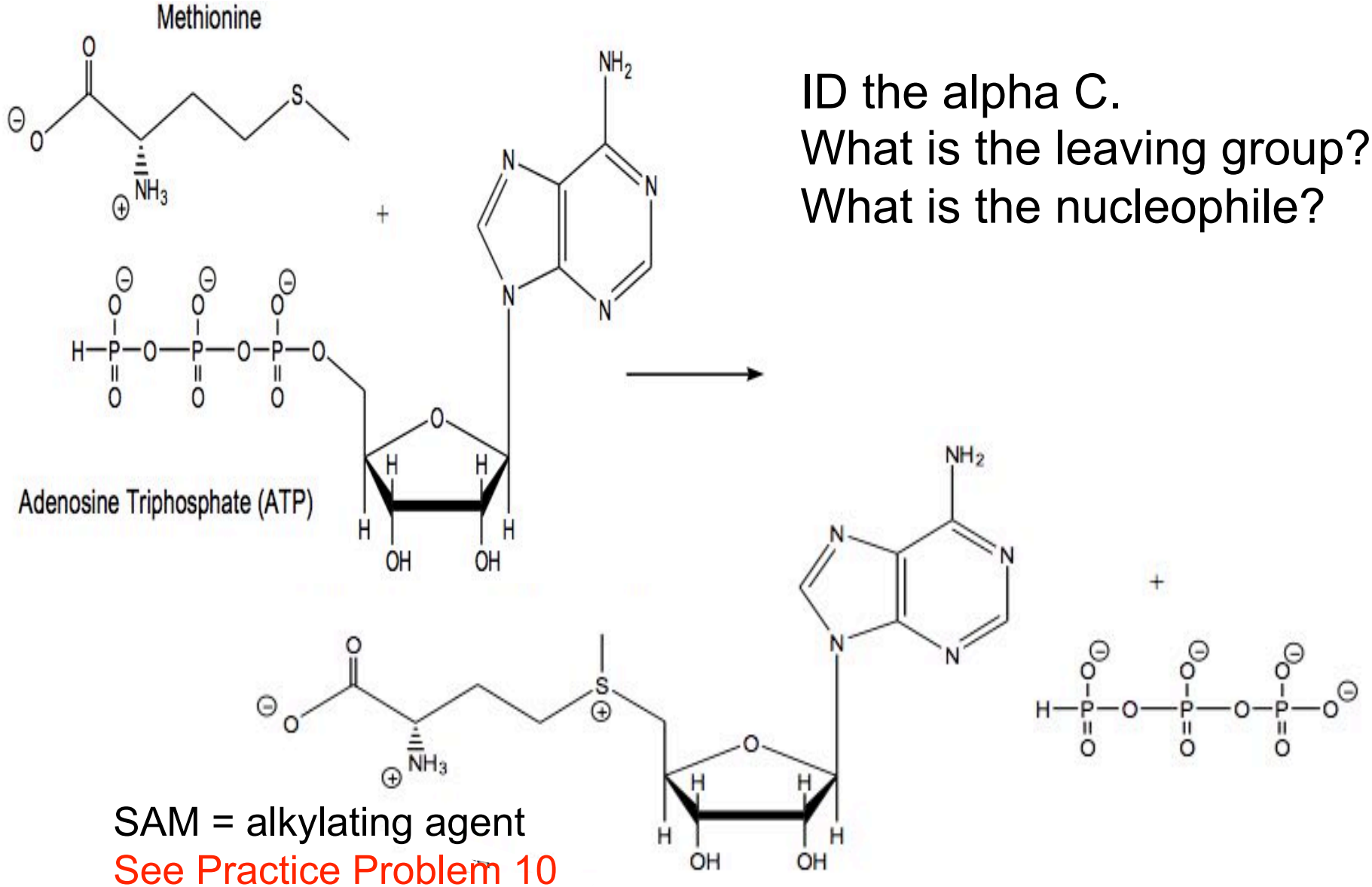
OH^- = strong base = _____ LG

H_2O = weak base = _____ LG

How can you convert C-OH to C-OH_2^+?

What type of reaction is this?

Substitution in **Biology**: Exchange (substitute) one atom or group for another on the same carbon

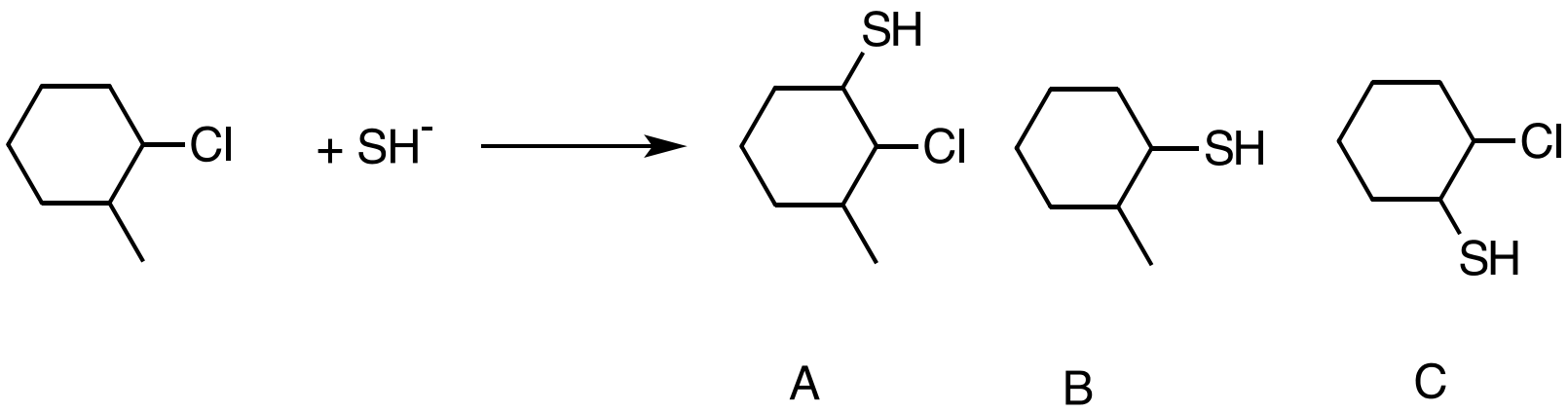


ID the alpha C.
What is the leaving group?
What is the nucleophile?

SAM = alkylating agent

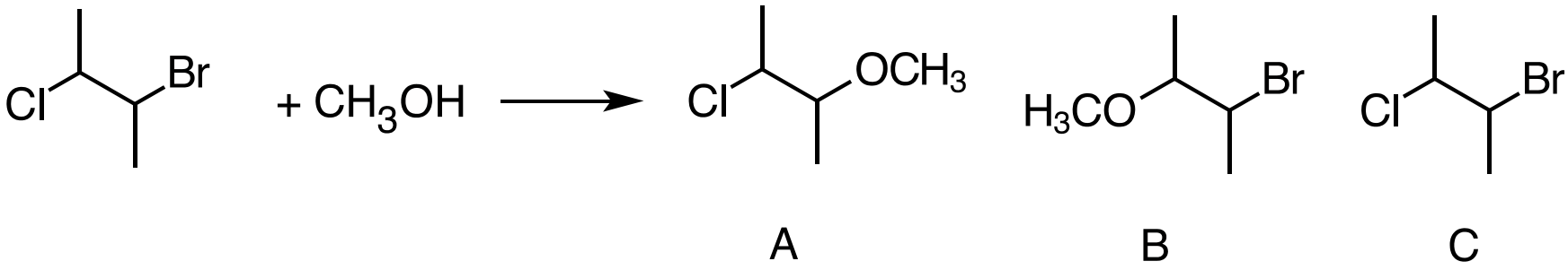
See Practice Problem 10

Objectives: Identify the α - C.
Identify the E^+ and the $Nu:^-$ and LG.
Predict the product(s).



A B C

Objectives: Identify the α - C.
Identify the E^+ and the $Nu:^-$ and LG.
Predict the product(s).

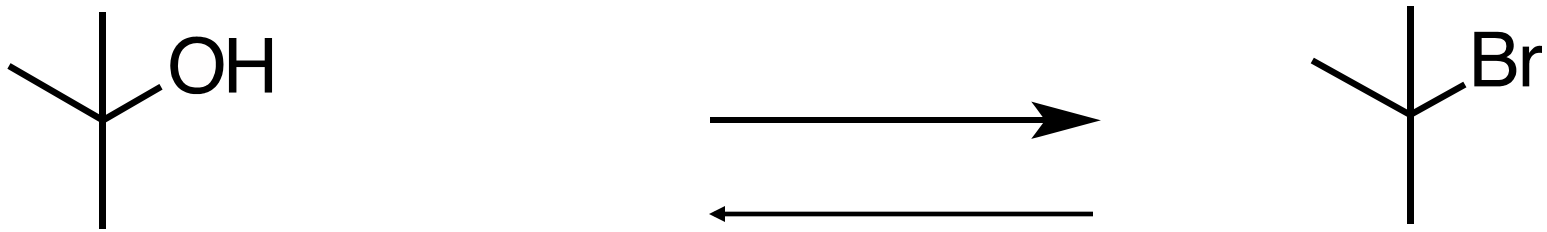


A B C

Explain the following observations:

$Cl^- + CH_3OH \rightarrow$ *No Reaction*

$HCl + CH_3OH \rightarrow CH_3Cl + H_2O$



Alcohol contains the OH group, which is a ____ LG.

Should -OH be made into a better LG?

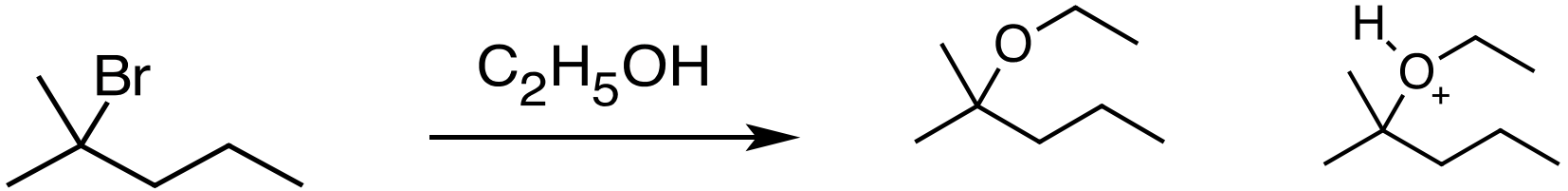
If so, how is -OH made into a better LG?

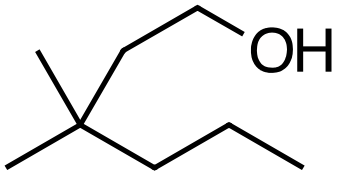
Which reagent will you use to convert the ROH to the RBr?

Which reagent will you use to convert the RBr to the ROH?

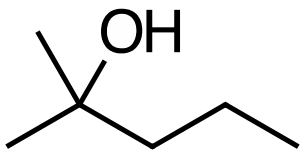
Common Mistakes

Objective: Given Reactants ==> Predict Products





How did C-C bond form?



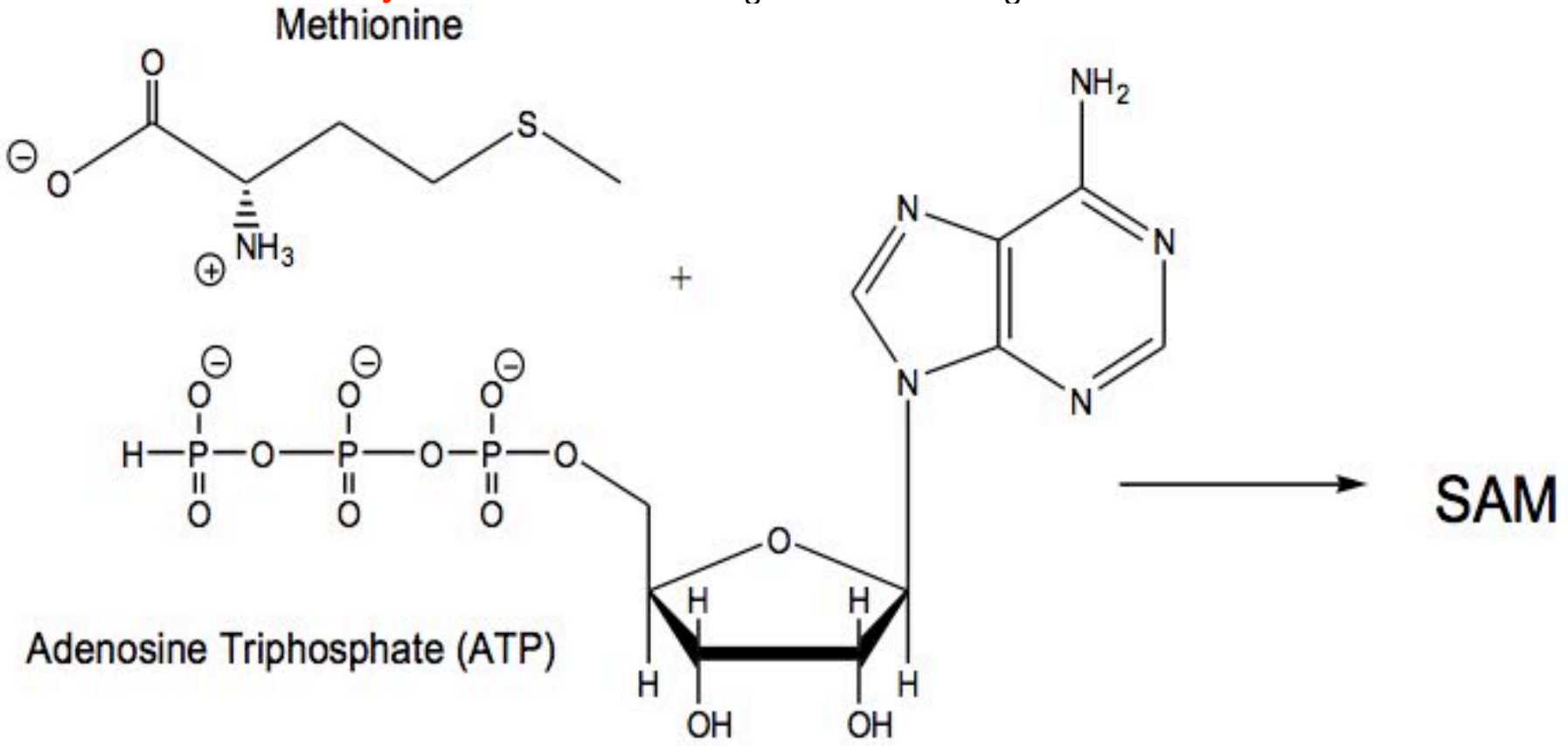
How did C-O bond break?

Incorrect bonding - use curved arrows **and** known bond making/breaking process

Substitution in Biological Systems

SAM is an Alkylating Agent

Alkylation: $Nu:^- + CH_3\text{-}I \rightarrow Nu\text{-}CH_3 + I^-$



Nucleophile = S in methionine. $Nu:^-$ reacts at C bonded to O bonded to P. Leaving group = triphosphate.

What is the structure of SAM?

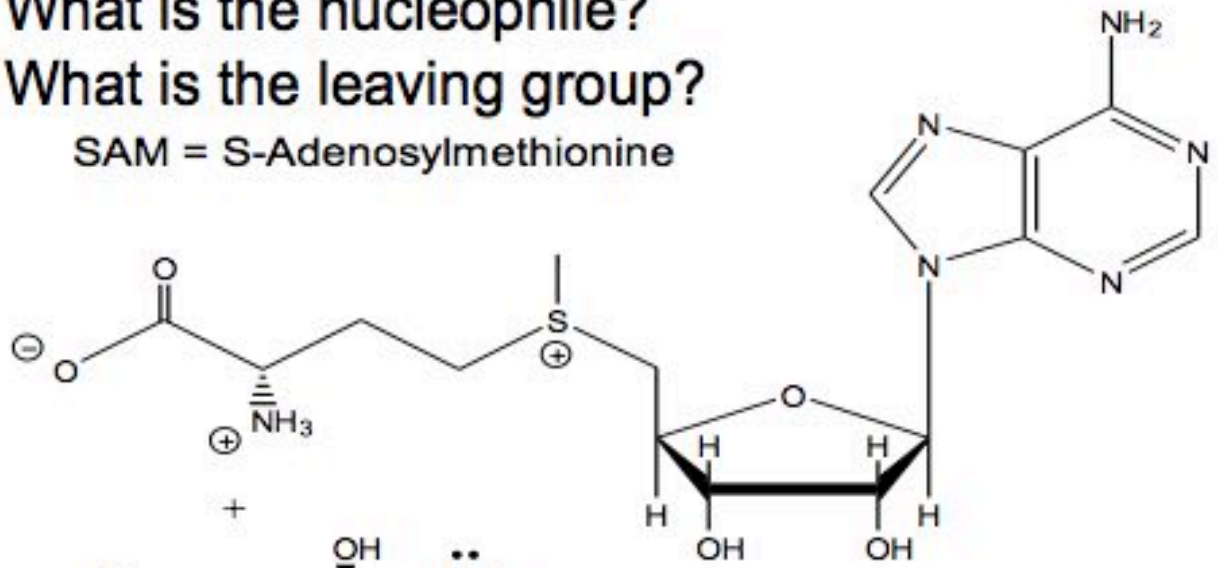
Substitution in Biological Systems

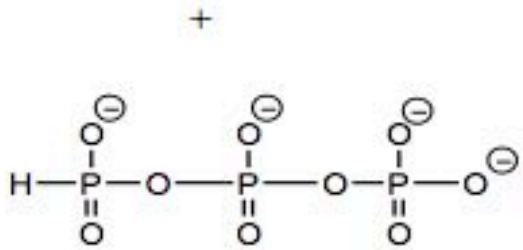
SAM is an Alkylating Agent: What is the substrate?

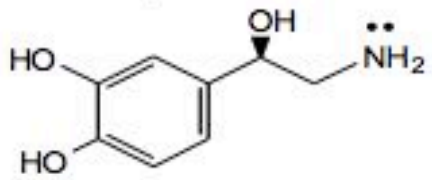
What is the nucleophile?

What is the leaving group?

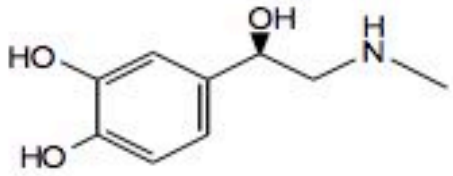
SAM = S-Adenosylmethionine







Noradrenaline

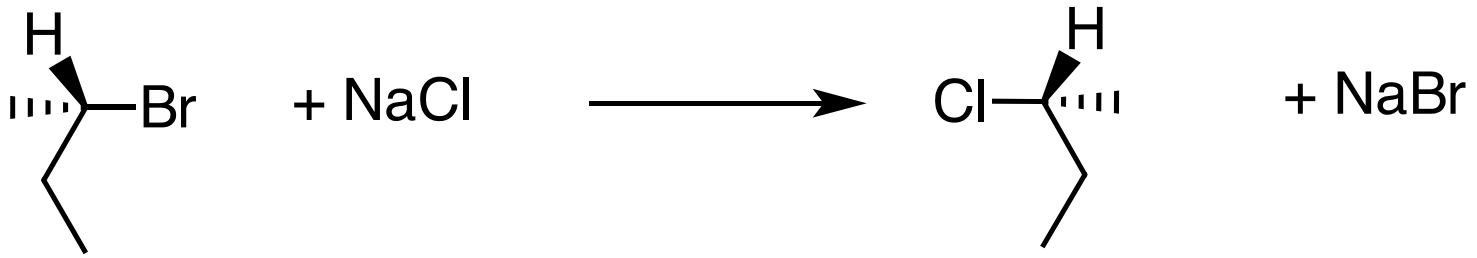


Adrenaline

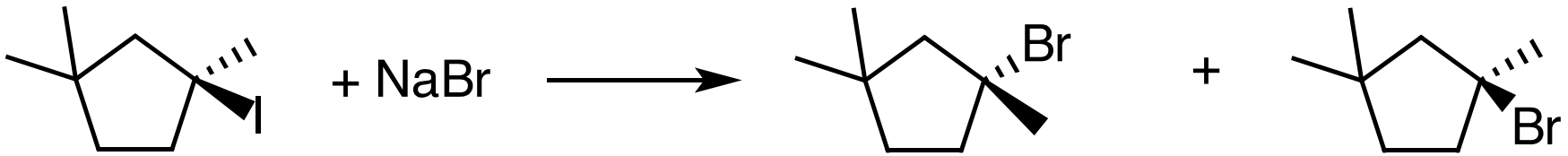
See Practice Problem 10

Reference: Klein, "Organic Chemistry", Wiley, 2011, p. 296

Explain the following observations: (Klein, p. 301-302)



(S)-2-bromobutane (R)-2-bromobutane



50% 50%

Use Reaction Mechanism to:

- Explain why a product forms

- Explain product distribution (major and minor products)

- Choose conditions for a reaction if you want a specific stereochemical product.

Explain or Predict the Major and Minor Reaction Products With a ***Reaction Mechanism***

Experiment --> Rate law --> Reaction mechanism
Reaction mechanism: sequence by which bonds break and form going from reactants to intermediates to products.
Rate determining step: slowest step in mechanism
Stability of intermediate or product helps you determine product distribution.

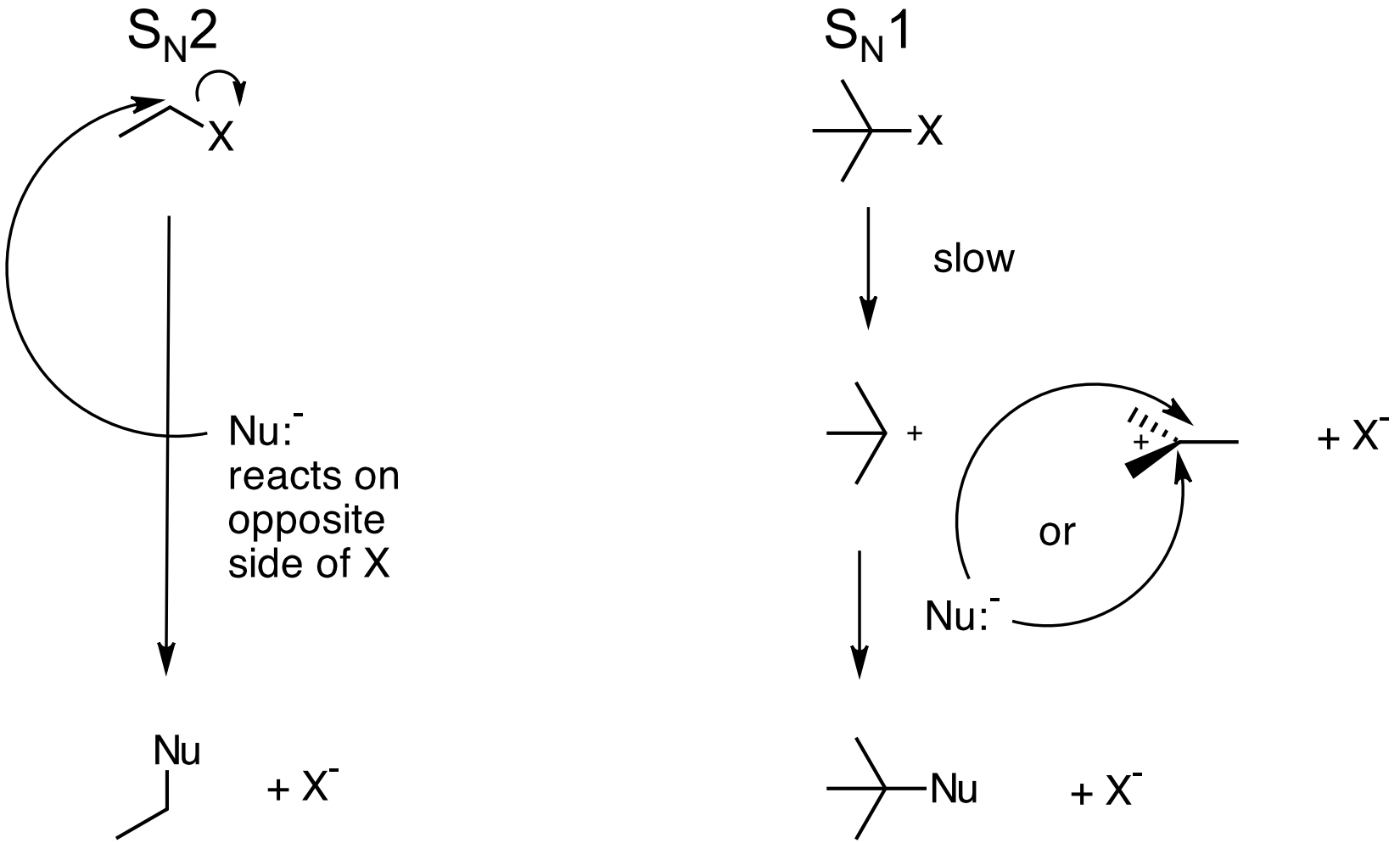
Use "curved arrows" to show bonds breaking and forming in each elemental step.

For polar reactions:
$Nu:^-$ reacts with E^+
Draw curved arrow from $Nu:^-$ to E^+

2 Substitution Reaction Mechanisms: S_N1 and S_N2

Does C-Nu bond form first?
Or Does C-LG bond break first?
Or Does the C-Nu bond form and C-LG bond break simultaneously?
How is stereochemistry affected?

Two types of Substitution reaction mechanisms to explain RX reactivity:



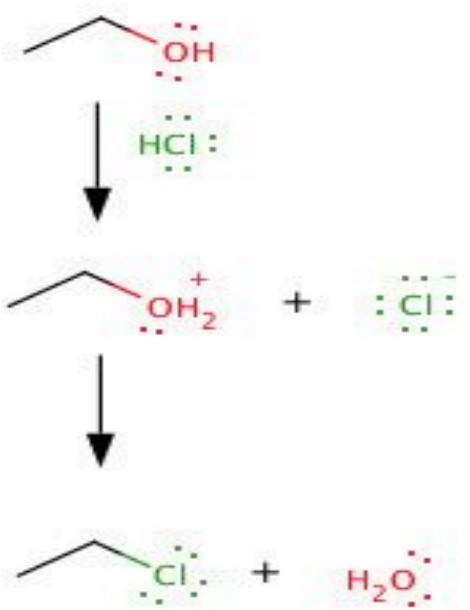
Draw a reaction energy diagram.

Use curved arrows to show bonds breaking and forming.

Draw a reaction energy diagram.

Two types of Substitution reaction mechanisms to explain ROH reactivity:

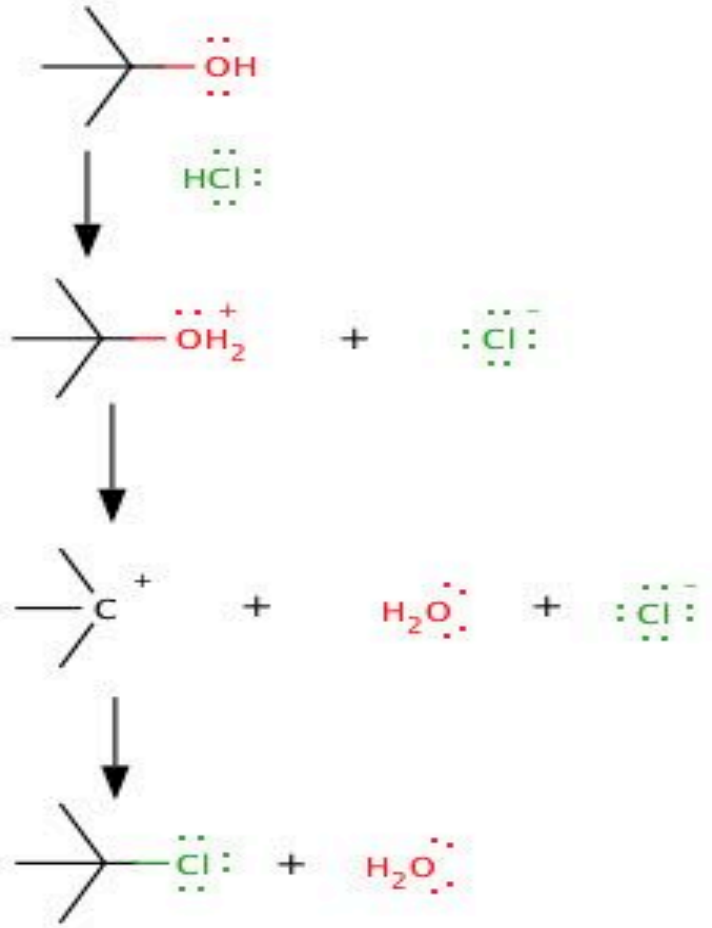
S_N2



fast

slow

S_N1



fast

***What does the "1" in S_N1 mean*?**

Rate determining (slow) step: **loss of leaving group**

Rate law: rate = k [R-LG] involves 1 substance

[Nu:$^-$] does not affect rate

***What does the "2" in S_N2 mean*?**

Rate determining (slow) step: **Nu:$^-$ attack on α-C**.

Rate law: rate = k [R-LG][Nu:$^-$] involves 2 substances

[Nu:$^-$] does affect rate

Effect of Substrate (RX or ROH)

Substrate is the Reactant with a Leaving Group

1^o RX or ROH undergoes substitution reactions via S_N2

3^o RX or ROH undergoes substitution reactions via S_N1

2^o RX or ROH undergoes substitution reactions via either

(Does the substrate really care about the mechanism type?)

No - but you may care if you want to make a specific compound.

S_N1 Mechanism involves a Carbocation Intermediate

Need a 3° R-X or 3° ROH

Need a **Good Leaving Group** (LG) to form a carbocation
A good LG is a ***weak*** base.

Which is the best LG?

1. F^- Cl^- Br^- I^-

2. OH^- H_2O H_3O^+

S_N1 Mechanism involves a Carbocation Intermediate

3º Carbocations are More Stable than 2º C⁺ which are more stable than 1º C⁺. (1º C⁺ have not been observed)

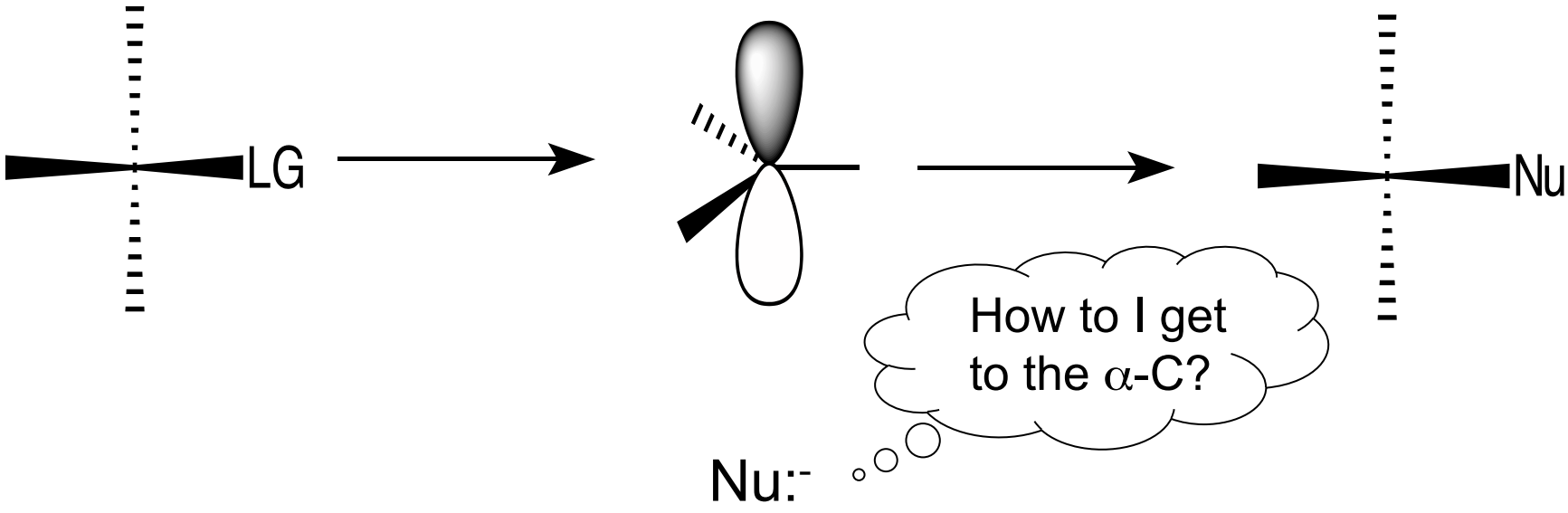
Stability due to hyperconjugation and inductive effects ==> R groups stabilize C⁺ better than H does.

What is the shape at the C⁺?

In what orbital is the (+) charge?

Does shape at C⁺ allow easier access to Nu:⁻?

By what path does Nu:⁻ get to C⁺?



S_N1 Mechanism involves a Carbocation Intermediate
The Stability of the Intermediate helps explain Product Distribution

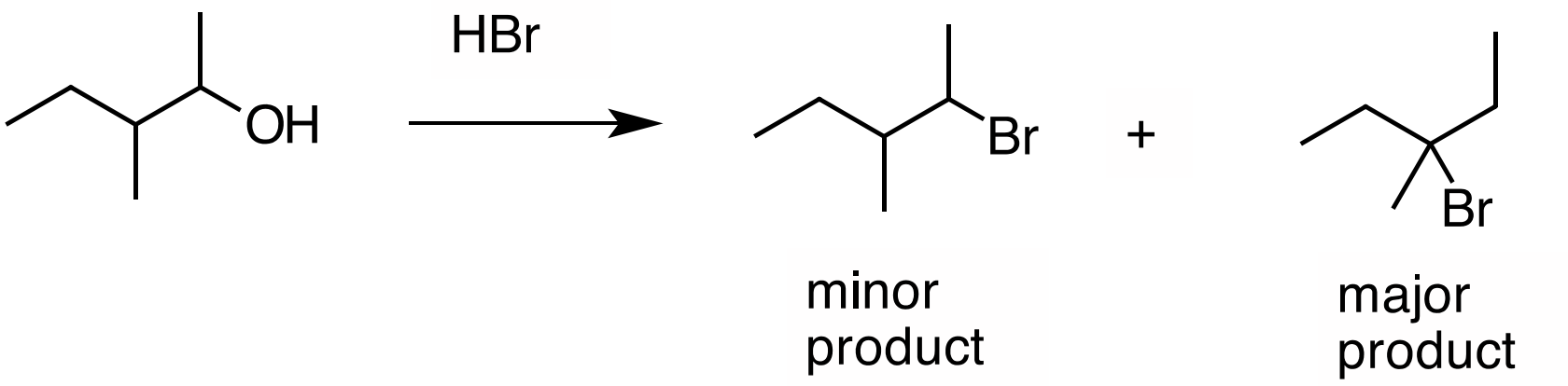
3^o C^+ > 2^o C^+ > 1^o C^+

3^o Carbocations are More Stable than 2^o C^+ which are more stable than 1^o C^+. (1^o C^+ have not been observed)

If you see 2^o C^+, check to see if a 1,2 rearrangement forms more stable 3^o C^+.

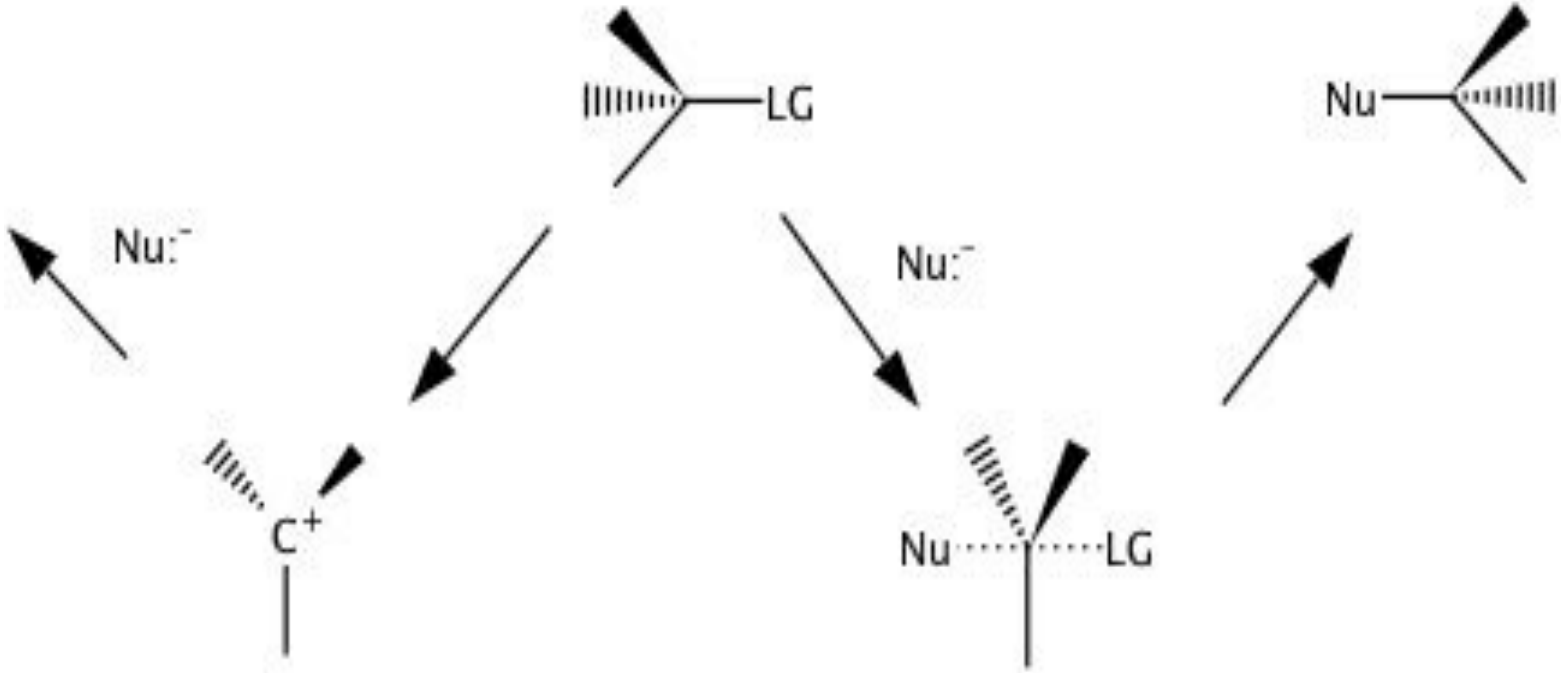
If you are planning a synthesis and want to minimize other products due to C^+ rearrangement, what substitution mechanism should you use?

Explain the following observations: (Klein, p. 308)

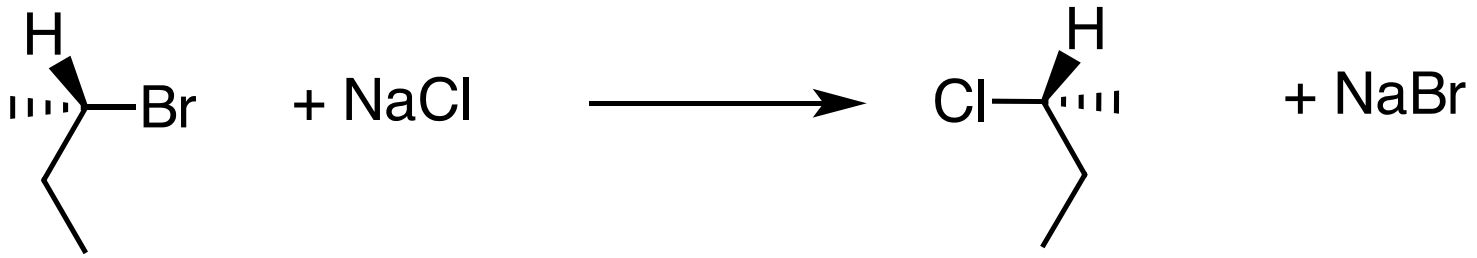


*The **Stereochemistry** of the Product is explained by the Substitution mechanism type* (S_N1 or S_N2).

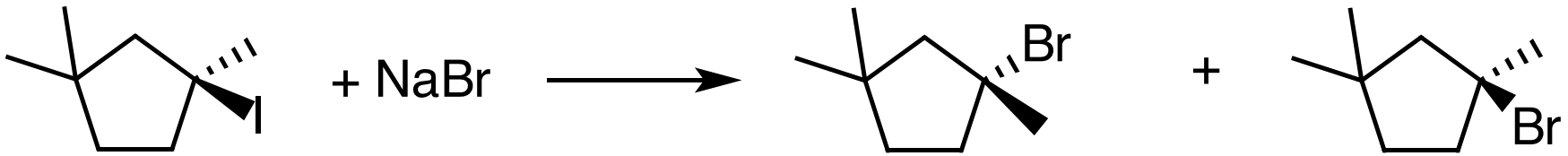
S_N1 Mechanism Produces a ***Racemic Mixture***.
S_N2 Mechanism Produces an ***Inversion in Configuration***.
By which path does the $Nu:^-$ react? What intermediate is formed?
What stereoisomer(s) are produced?
What is the reactivity of 1°, 2°, and 3° for each mechanism?



Explain the following observations: (Klein, p. 301-302)



(S)-2-bromobutane (R)-2-bromobutane



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Does the Substitution Mechanism really matter when I can predict the product?

OR

Do the Reactants really care if the Mechanism is S_N1 or S_N2?

You have an optically pure chiral 2° ROH. You want to convert the alcohol to an alkyl bromide and want to get an optically pure product.

What **<u>reaction conditions</u>** would you use?

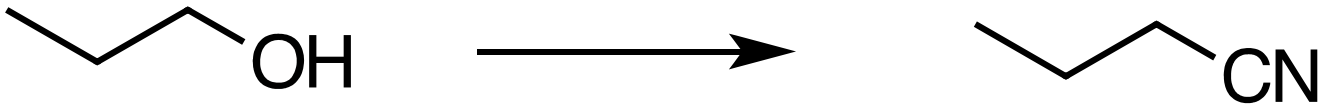
In other words, what $Nu:^-$ would you use?

What LG would you use?

What solvent would you use?

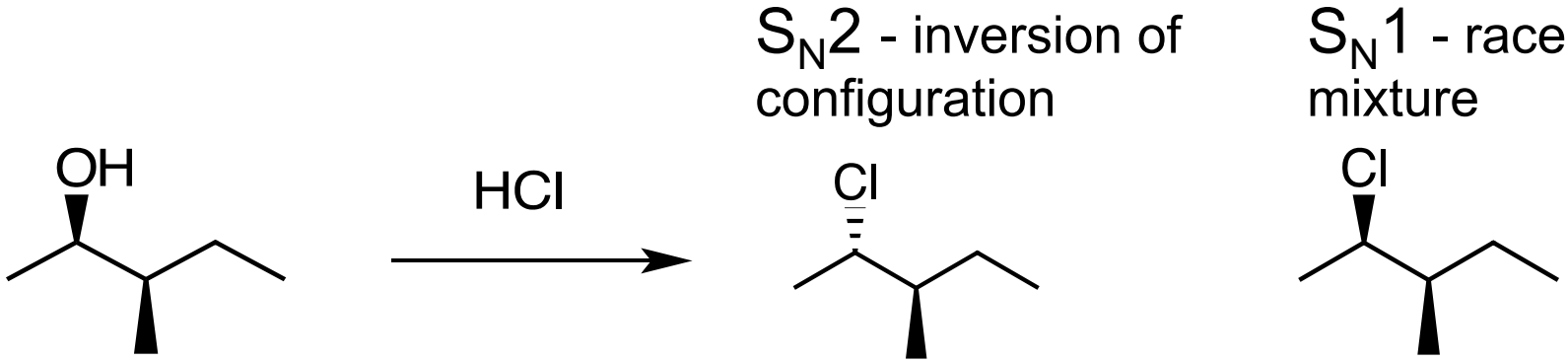
Common Mistakes

Given Reactants and Products ==> Determine reaction conditions



Did not remember -OH is a poor leaving group
Did not make -OH into a better leaving group (use acid)

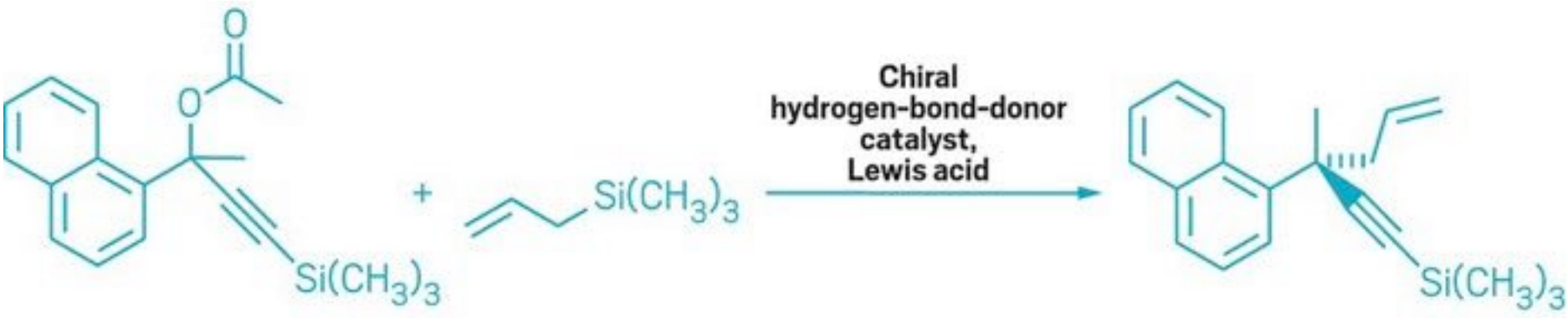
Relate mechanism to product



S_N2 - inversion of configuration

S_N1 - racemic mixture

"*Coaxing chirality from an S_N1 reaction*" (CEN, 4/30/18, p. 10)
S_N1 reactions are unpopular because chiral compounds become racemic mixtures. Chiral catalyst system converts racemic 3° compound into one enantiomer.

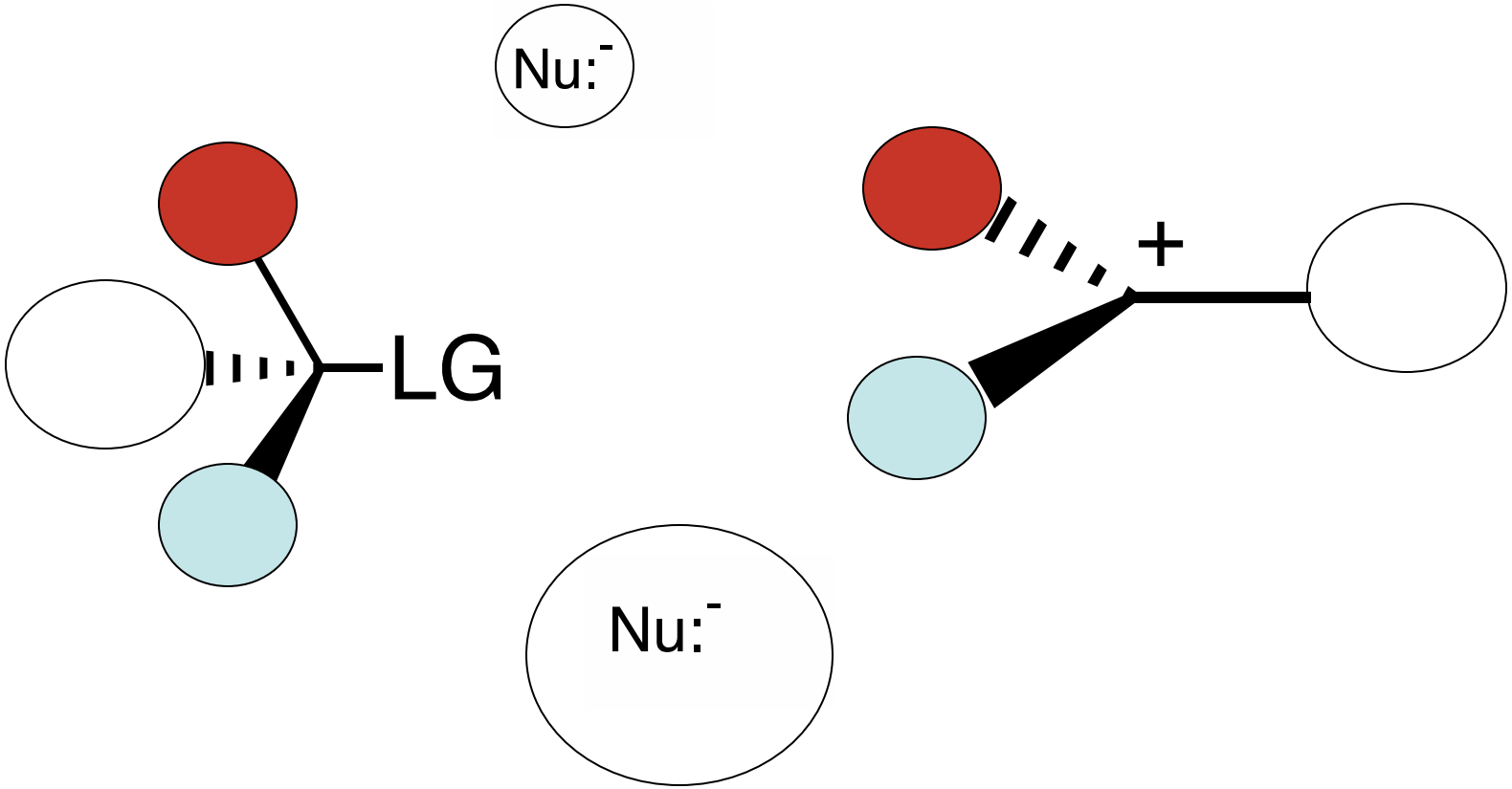


S_N1 mechanism but catalyst guides $Nu:^-$ approach to one side of the carbocation intermediate.
https://cen.acs.org/synthesis/catalysis/Coaxing-chiral-products-SN1-reaction/96/i18

Substitution Reaction:

At what atom does Nu:⁻ react?

What path does Nu:⁻ take to this atom?



How does the SOLVENT affect the Nu:⁻ or the substrate or intermediate?

Factors that Favor S_N1 and S_N2 (Klein, p. 320)

Factor	Favors S_N1	Favors S_N2
Substrate (RX or ROH)	3^o	Methyl or 1^o
Nucleophile	Weak	Strong
Leaving Group	Excellent LG	Good LG
Solvent	Polar protic	Polar aprotic
Stereochemistry	Racemic mixture	Inversion of configuration

(i) Choose Solvent in which Reactants Are Soluble and Not Reactive Towards Reactants

(ii) Solvent Affects Reaction Rate By Stabilizing the Intermediate

Solvent classification: Polarity (dielectric constant), Protic (capable of H-bonding), Aprotic (no H bonding)

Solvent	Formula	Type
Acetic Acid	CH_3COOH	Polar, protic
Methanol	CH_3OH	Polar, protic
Water	H_2O	Polar, protic
Acetone	$(CH_3)_2CO$	Polar, aprotic
Acetonitrile	CH_3CN	Polar, aprotic
DMSO	$(CH_3)_2SO$	Polar, aprotic
DMF	$(CH_3)_2NCHO$	Polar, aprotic

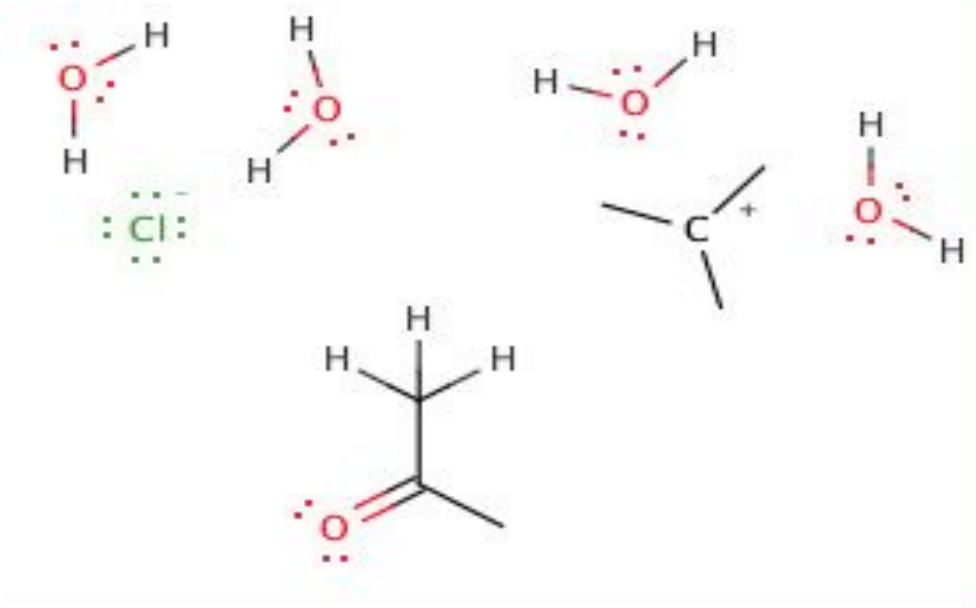
(See Carey, "Organic Chemistry", 8th ed., p. 341, Table 8.6)

Nu:$^{-}$ are *More Reactive* in *Aprotic Solvents* than Protic Solvents

Polar, *Protic* Solvents can Solvate Reactants, e.g., Cl^- ==> Makes Reactants Stable (Less Reactive).

Polar, *Protic* solvents help S_N1 (3^o RX) ==> Stabilizes C^+ intermediate.

Water surrounds Cl^- (like a bodyguard) and doesn't allow it to react



Polar, *Aprotic* Solvents Do Not Solvate (Less) Reactants, e.g., Cl^- ==> Makes Reactants *More* Reactive.

Polar, *Aprotic* solvents help S_N2 (1^o RX) ==> no Nu:$^{-}$ solvation

Nucleophilic Substitution Reactions

Reaction 1: R-X + NaI -- acetone ---> R-I + NaX (s)

Reaction 2: R-X + $AgNO_3$ -- ethanol ---> R^+ + AgX (s)

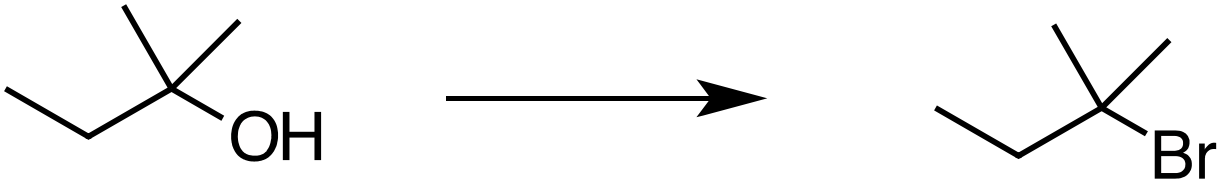
Acetone is a polar, aprotic solvent
Ethanol is a polar, protic solvent
$Nu:^-$ are less solvated in acetone than ethanol
$Nu:^-$ are more reactive in acetone than ethanol
Less solvated $Nu:^-$ in acetone ==> easier access to α-C ==> helps S_N2 reaction
R^+ is stabilized by ethanol ==> ethanol helps S_N1 reaction

Which R-X should occur via Reaction 1?
Which R-X should occur via Reaction 2?

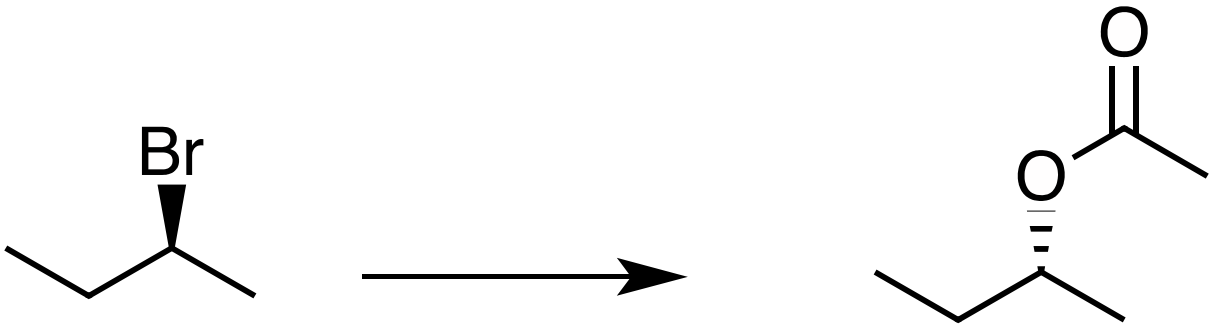
Synthesis: *Convert one Functional Group to Another*

Determine the reaction conditions (reagents, solvents) for each reaction: (Klein, "Organic Chemistry", 1st ed., Problem 7.59)

a.



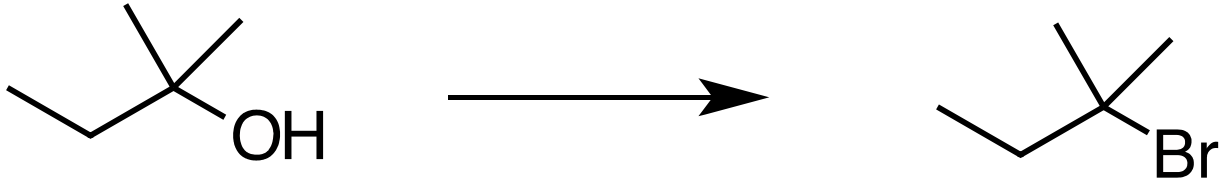
b.



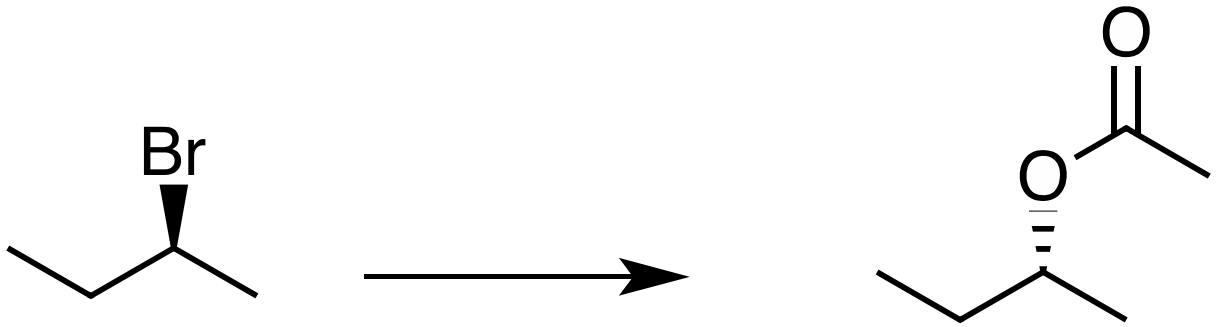
Synthesis: *Convert one Functional Group to Another*

Determine the reaction conditions (reagents, solvents) for each reaction: (Klein, "Organic Chemistry", 1st ed., Problem 7.59)

3° ROH
S_N1 conditions
HBr
Polar, protic solvent

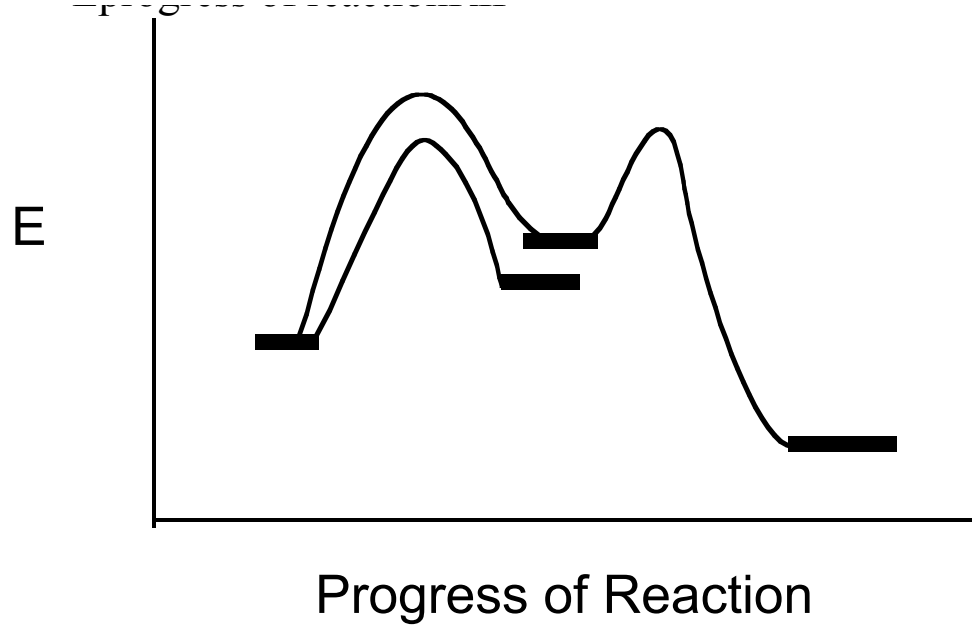


2° RX
Inversion of config
S_N2 conditions
Polar, aprotic solvent

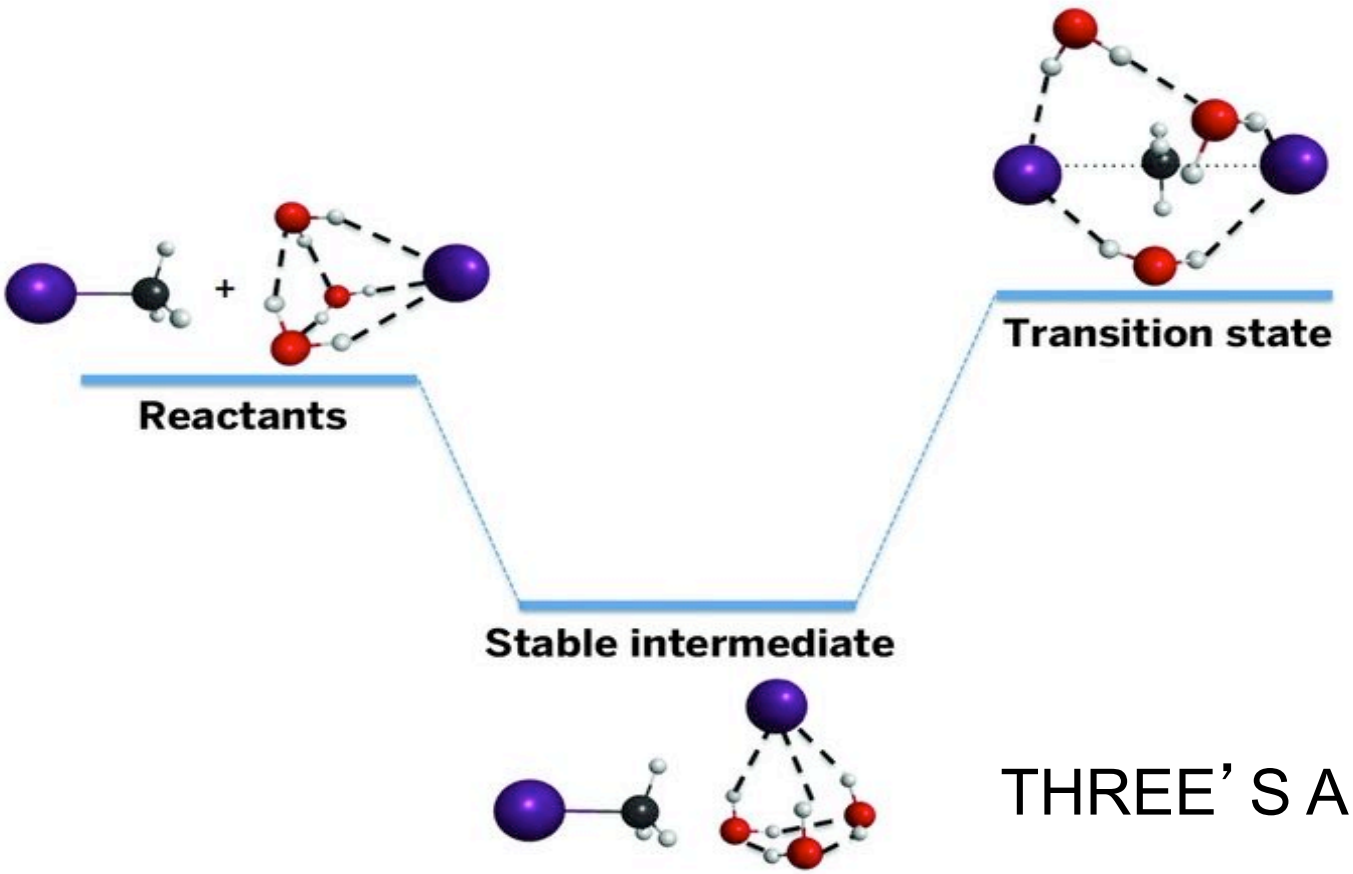


1. We've used CH_2Cl_2, ether, THF, and ethanol as solvents in lab.
a. Which solvent stabilizes a reactant or intermediate?
b. Which solvent would you use in 1-butanol --> 1-butylbromide?
c. Which solvent would you use in t-butyl bromide --> t-butyl bromide?

2. See Reaction Energy Diagram:
More stable intermediate → lower E → faster reaction
Does this diagram represent a S_N1 or S_N2 mechanism?



"Why S_N2 Reactions Don't Work in Water" (CEN, 2/25/13, p. 34)



THREE'S A CROWD

A CH_3I-water cluster study shows **just three water molecules** (red and white) **effectively crowd I^-** (purple) making the energy barrier from a stable intermediate to the transition state prohibitively high. (http://cen.acs.org/articles/91/i8/SN2-Reactions-Dont-Work-Water.html)