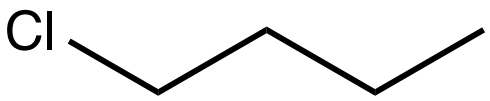
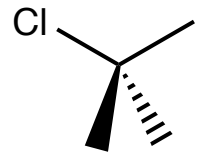
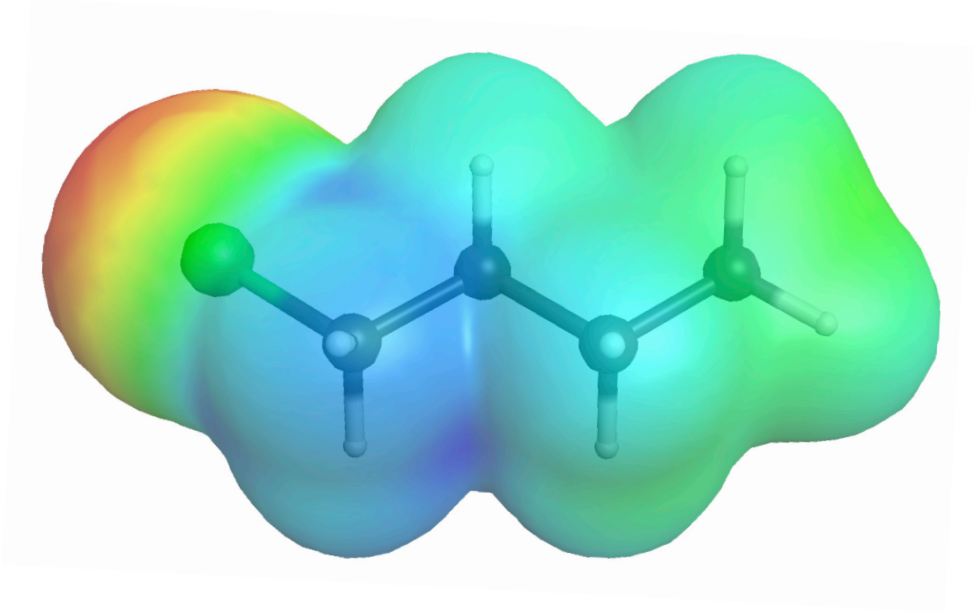
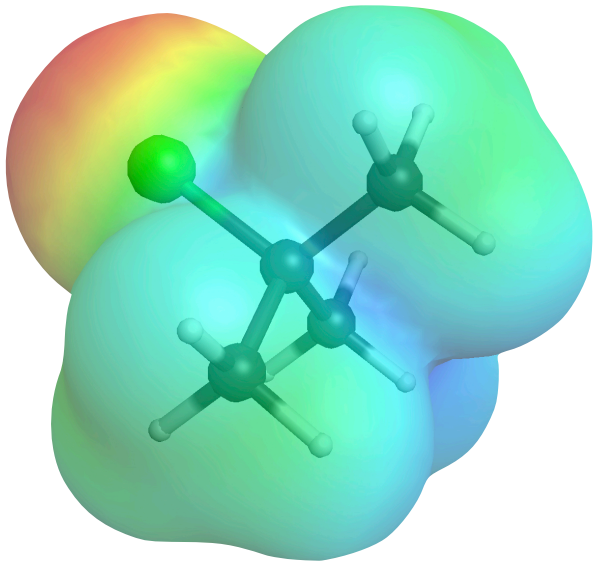
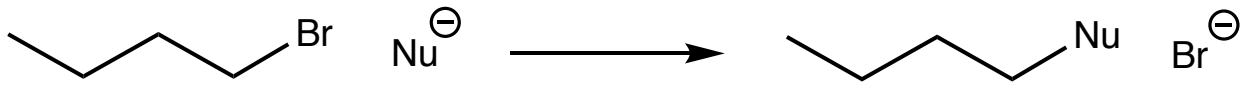
Reactivity of Alkyl Halides

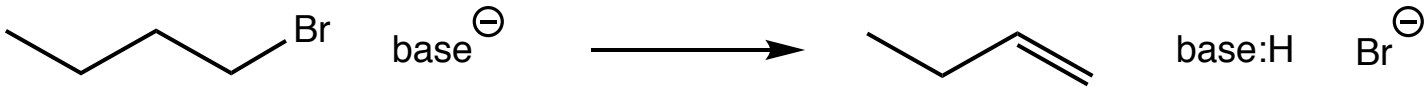









Br
Nu⊖
Nu
Br⊖


Br
base⊖
base:H
Br⊖

Overview

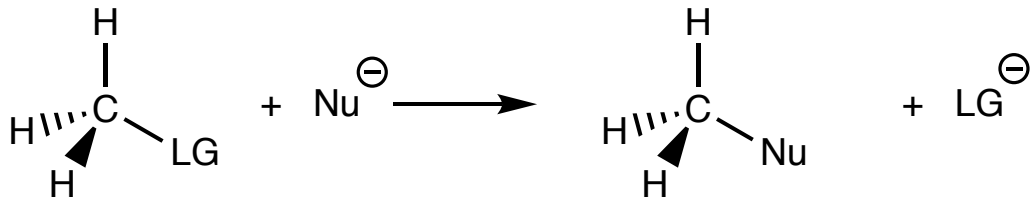
Nucleophilic Substitution and Mechanisms of Nucleophilic substitution: predict products and draw mechanisms

- Factors affecting nucleophilic substitution: describe and explain
- Competition between S_N1 and S_N2 Mechanisms: predict likely predominant mechanism
- Alcohols as Substrates in Substitution Reactions: predict products and describe reactions

Elimination Reactions and Mechanisms of Elimination Reactions

- Factors affecting elimination reactions
- Competition between E1 and E2 Mechanisms
- Alcohols as Substrates in Elimination Reactions

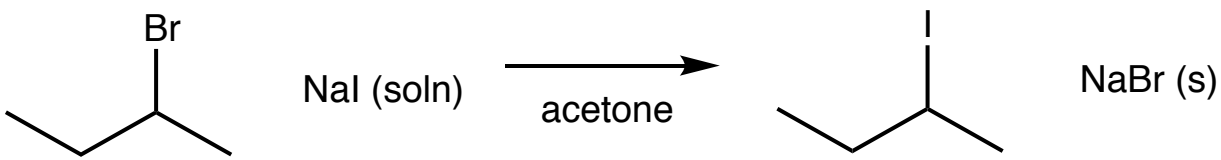
Competition between Substitution and Elimination Reactions



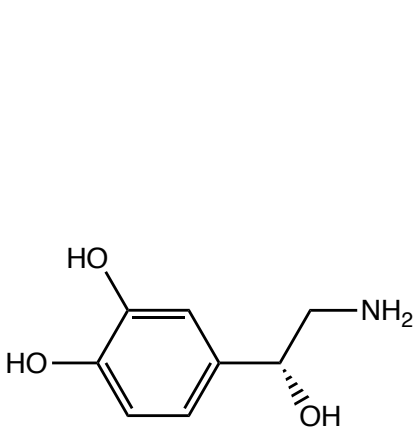
α-Carbon

Nucleophile

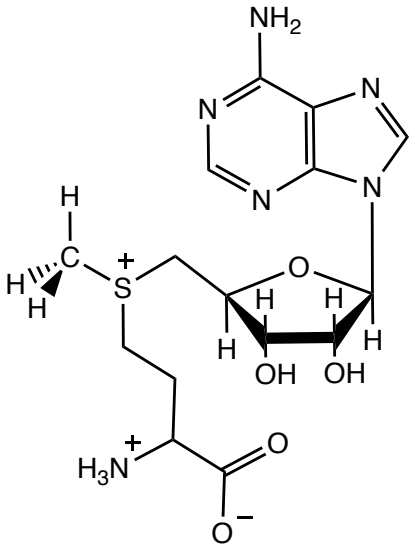
Leaving Group



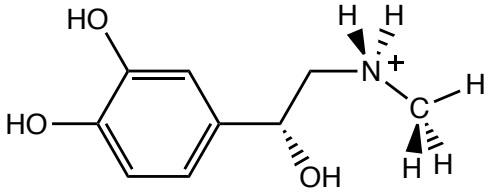
Nucleophilic Substitution Reactions in Biology



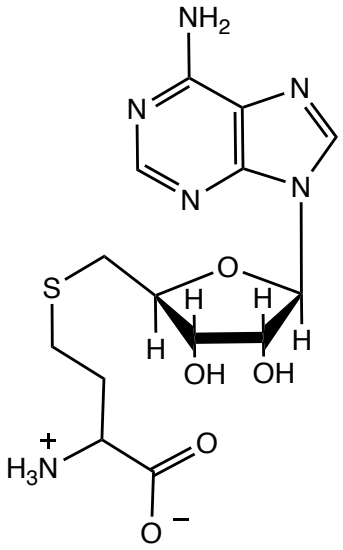
norepinephrine
(noradrenaline)



S-adenosylmethionine



epinephrine
(adrenaline)



Nucleophilic Substitution Reactions in Biology

The lysozyme mechanism sorted — after 50 years

Anthony J Kirby

Unambiguous evidence for a glycosyl-enzyme intermediate on the lysozyme reaction pathway has recently been reported, finally settling what kind of mechanism this textbook enzyme uses.

The publication in 1965[1] of the hen egg white lysozyme crystal structure — the first such structure of any enzyme — was a major landmark, offering the prospect of detailed explanations of enzyme mechanisms at the molecular level. Such mechanisms involve some of the most subtle relationships between structure and function in all of biology, as enzymes have to recognize and thus stabilize transition states, which probably exist for only femtoseconds. Because the structure of lysozyme was a first, and because of the coherent messages the structure seemed to provide, lysozyme has been a textbook example of enzyme mechanism ever since. Now, in a recent issue of *Nature*, Vocadlo *et al.*[2] report new evidence about the mechanism of lysozyme, information that has been sought after for almost 50 years.

Lysozyme is the most prominent member of the very large class of glycosidases or glycohydrolases, enzymes that catalyze the transfer of a glycosyl group to water. *In vivo* lysozyme catalyzes the hydrolysis of a polysaccharide component of the cell wall of Gram-positive bacteria. To do this it accelerates enormously the extraordi-

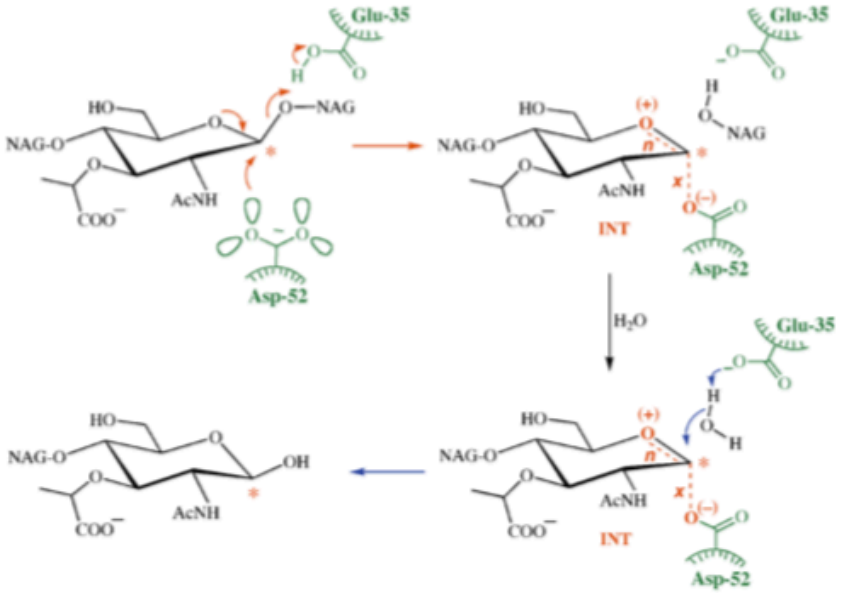
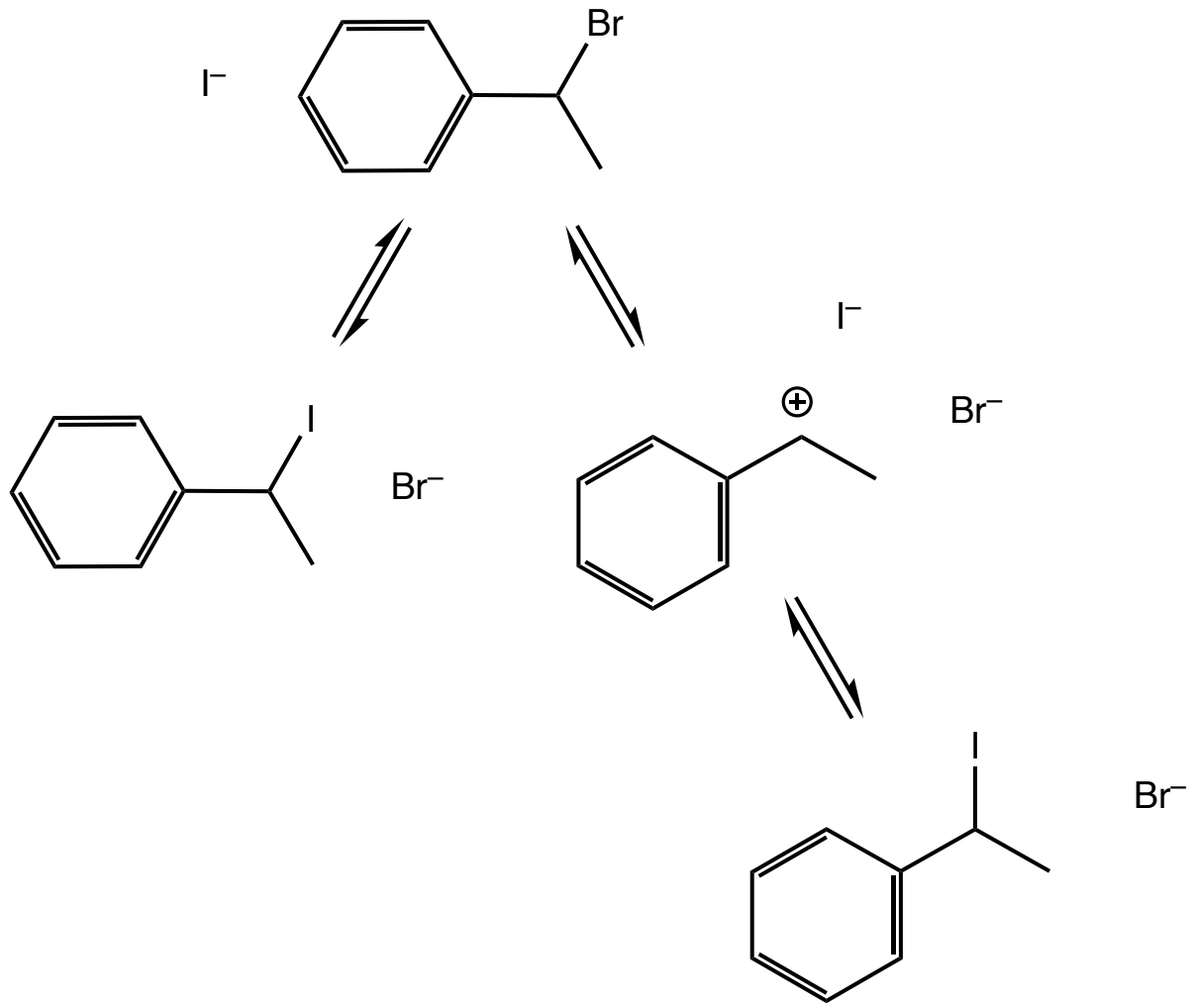
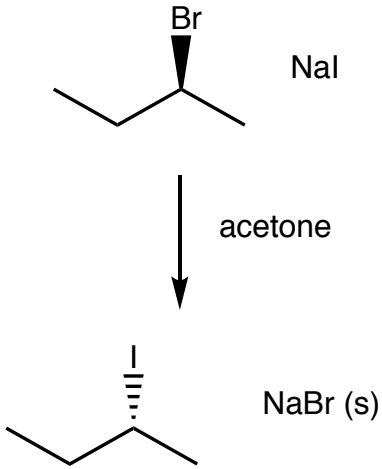


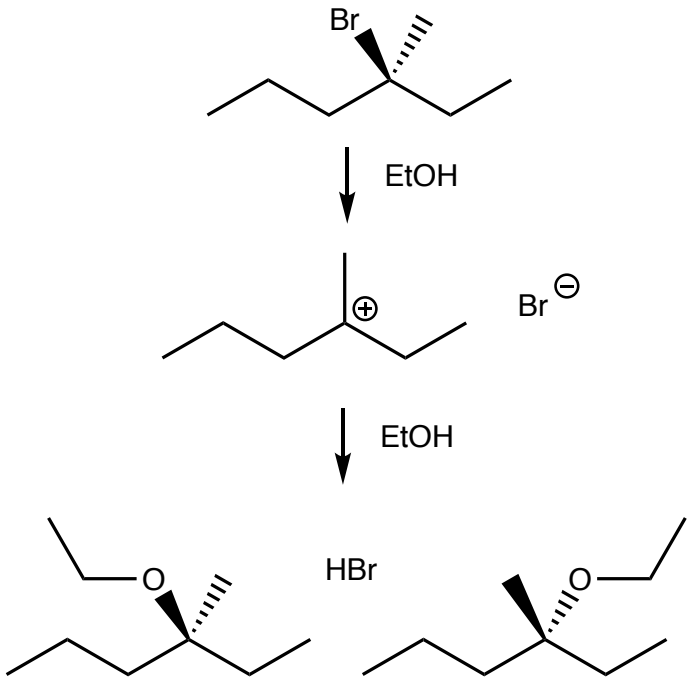
Fig. 1 The reaction catalyzed by lysozyme. The substrate is bound so that the leaving group oxygen, the 4-OH group of an N-acetylglucosamine (NAG) residue, is protonated as it leaves by the COOH group of Glu 35. Groups on the enzyme are colored green, electron movements and the key developing bonds and charges in red. Only one of the dashed *exo* and *endo* (*x* and *n*) bonds of the intermediate (INT) is actually present: which one defines the mechanism. Thus *n* is missing in mechanism (i), *x* in mechanism (ii).

Nature structural biology (2001), v8(9), p73

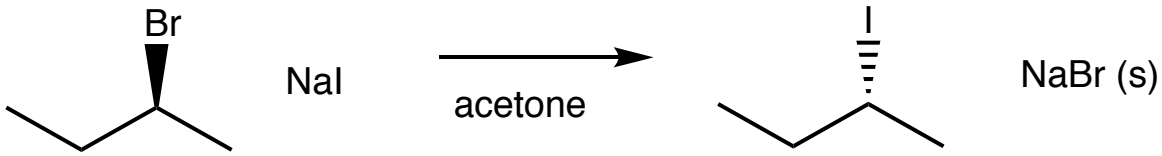

Br
I⁻
I⁻
I
Br⁻
Br⁻
I
Br⁻

Evidence for S_N2 and S_N1

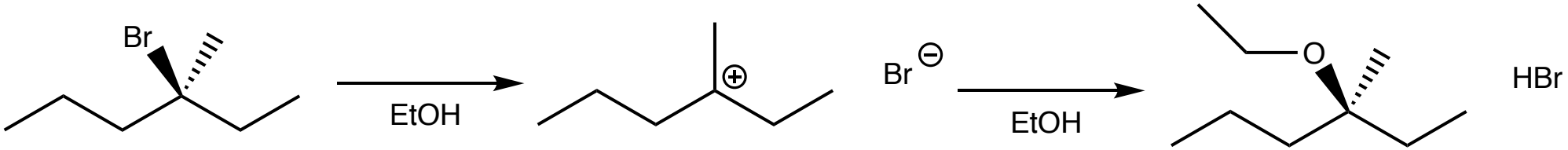




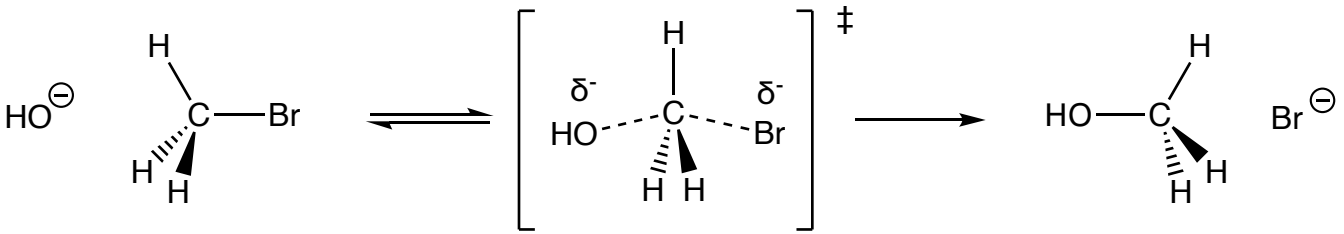
Evidence for S_N2 and S_N1

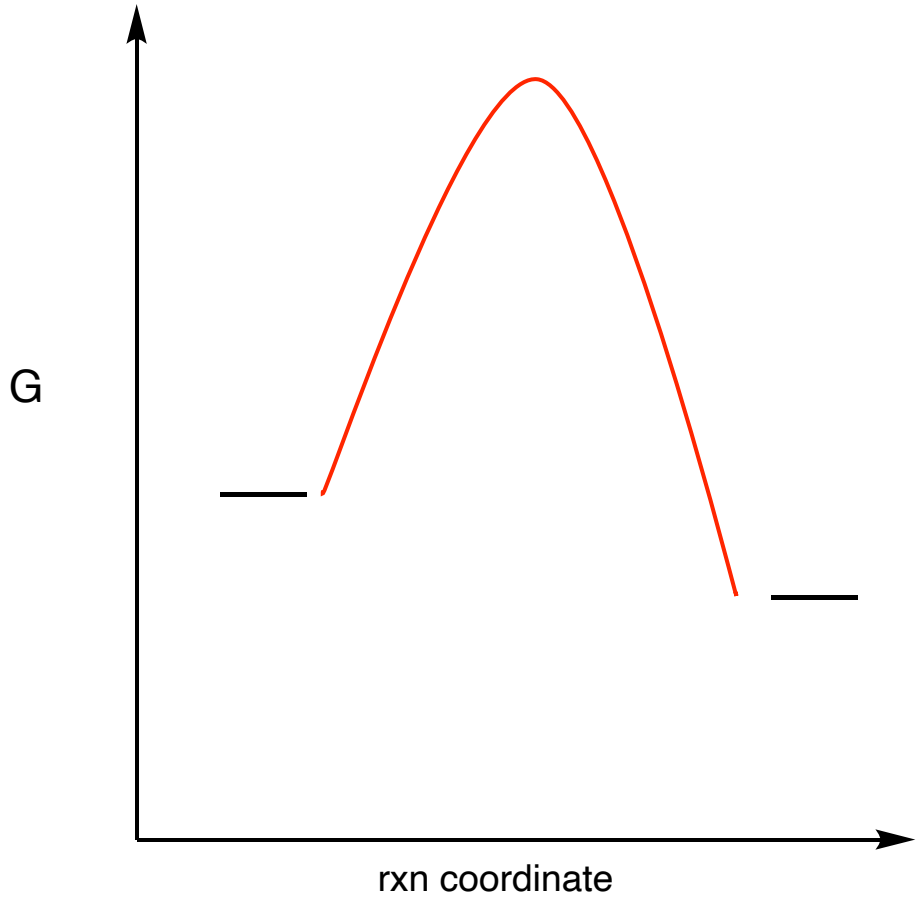


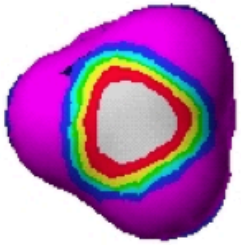
rate = k [$CH_3CH_2CH_2CH_2Br$][I^-]

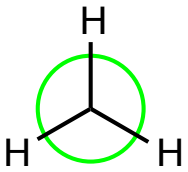


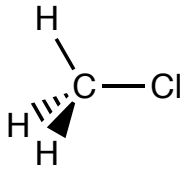
rate = k [$CH_3CH_2CH_2C(CH_3)BrCH_3$]

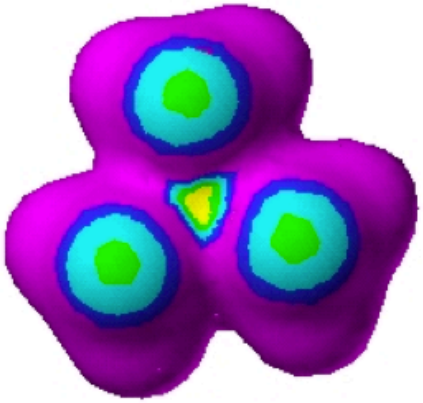

HO⊖
H
C
Br
H
H
δ-
δ-
HO
Br
‡
HO
Br⊖

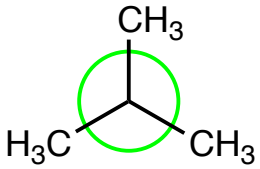

G
rxn coordinate

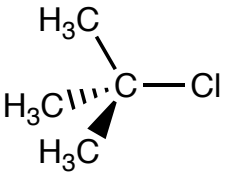



H
H
H


H
C
Cl
H
H

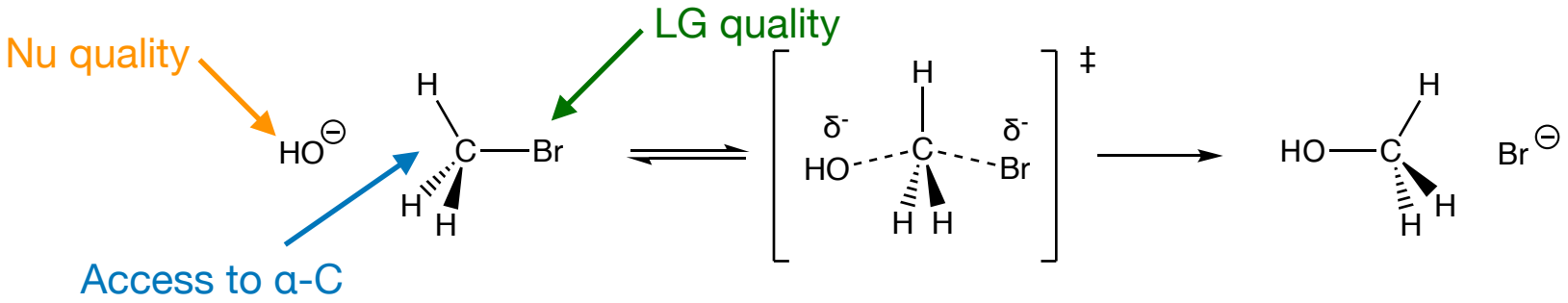


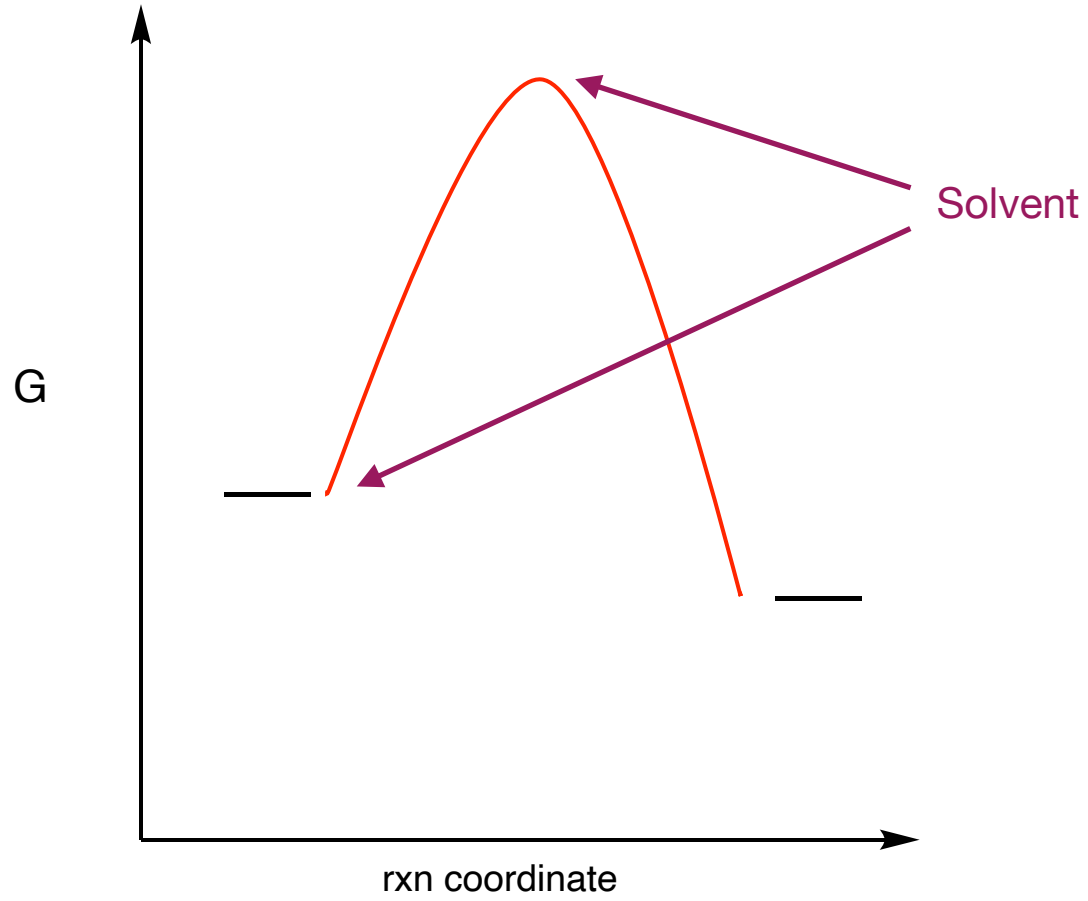

CH3
H3C
CH3

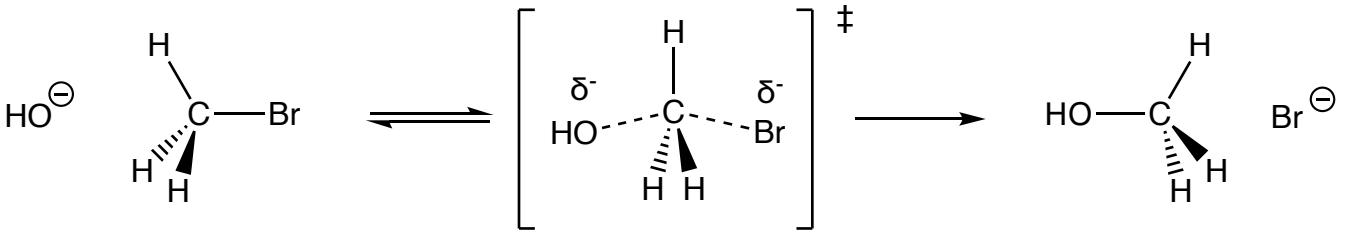

H3C
C
Cl
H3C
H3C

Factors Affecting S_N2 Reactions

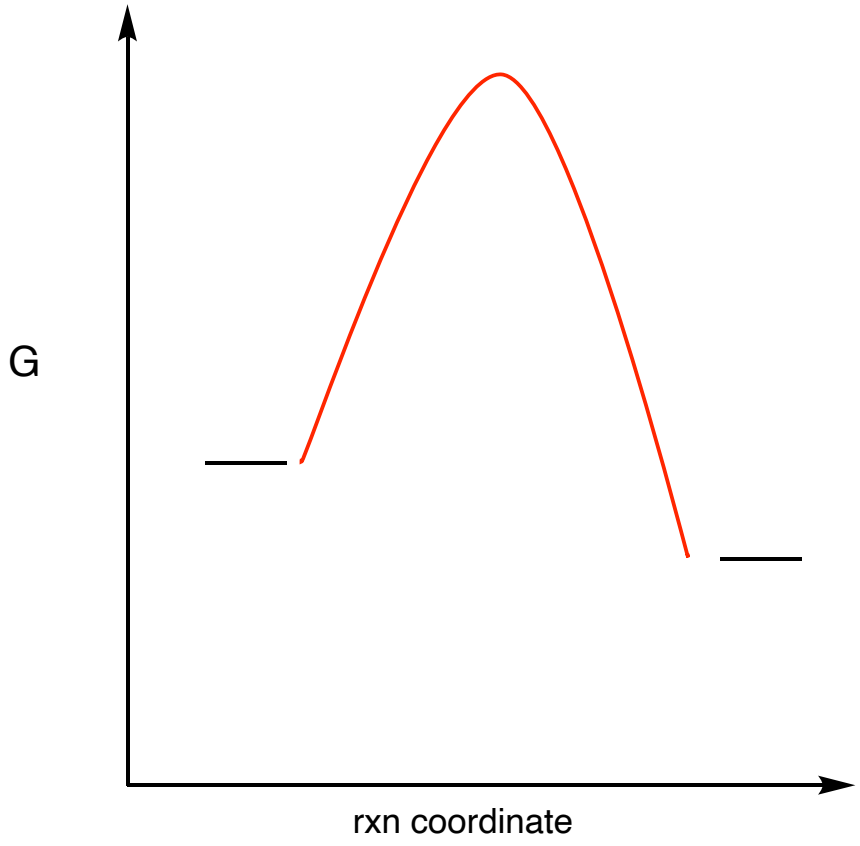
Section 11.2 and 11.3







rate = k [$CH_3CH_2CH_2CH_2Br$][Nu^-]



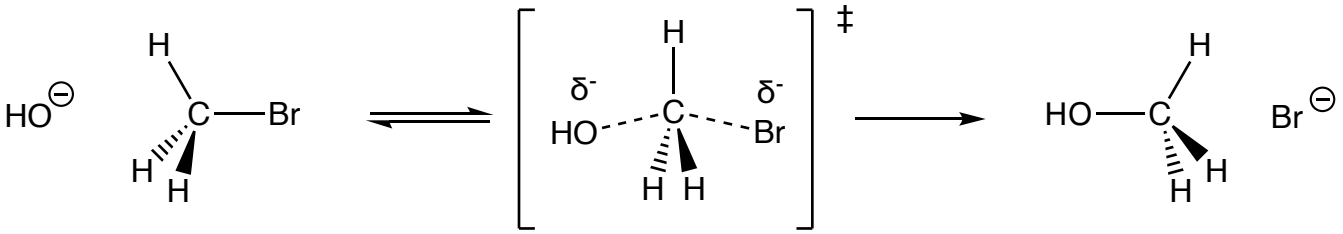
Factors affecting S_N2: Nucleophile Quality

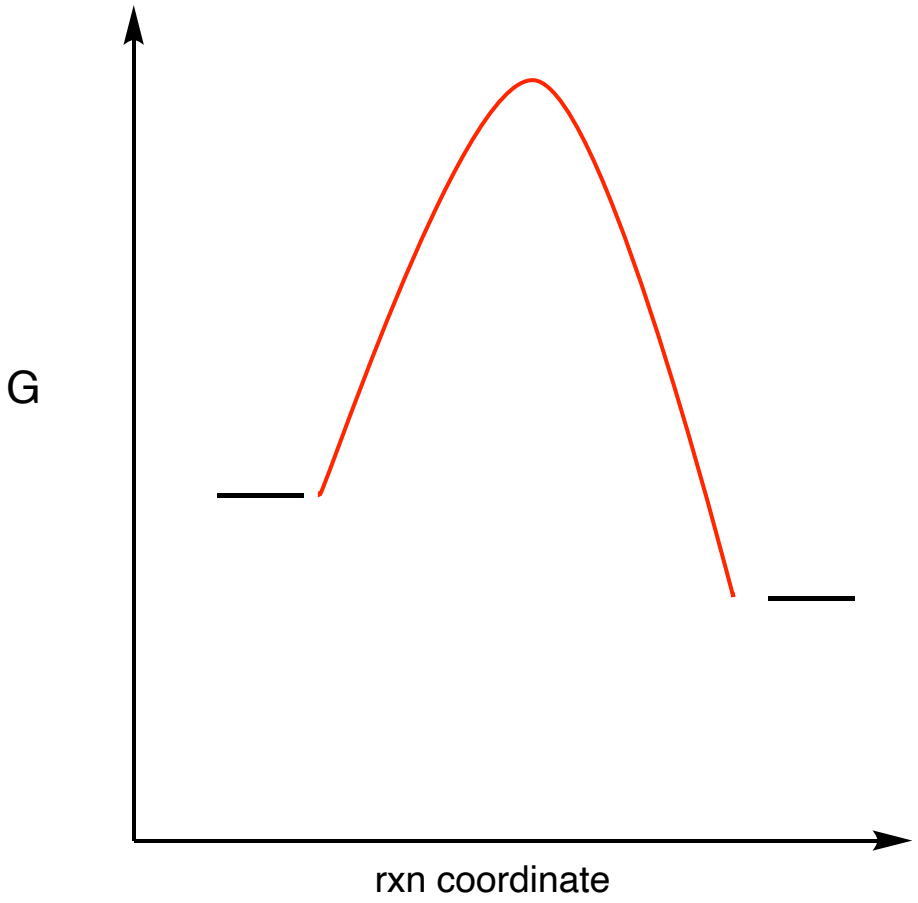
$$Nu:^- + CH_3Br \rightarrow CH_3Nu + Br^-$$

Nucleophile		Product		Relative rate of reaction
Formula	Name	Formula	Name	
H_2O	Water	$CH_3OH_2^+$	Methylhydronium ion	1
$CH_3CO_2^-$	Acetate	$CH_3CO_2CH_3$	Methyl acetate	500
NH_3	Ammonia	$CH_3NH_3^+$	Methylammonium ion	700
Cl^-	Chloride	CH_3Cl	Chloromethane	1,000
HO^-	Hydroxide	CH_3OH	Methanol	10,000
CH_3O^-	Methoxide	CH_3OCH_3	Dimethyl ether	25,000
I^-	Iodide	CH_3I	Iodomethane	100,000
^-CN	Cyanide	CH_3CN	Acetonitrile	125,000
HS^-	Hydrosulfide	CH_3SH	Methanethiol	125,000

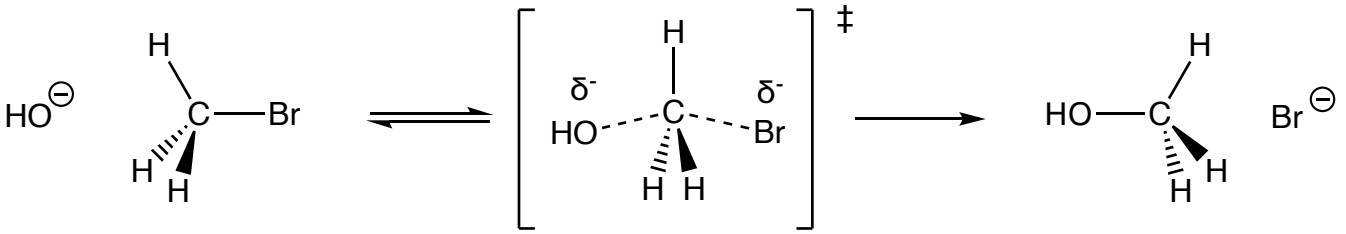
Organic Chemistry, a Tenth Edition. McMurry, OpenStax.

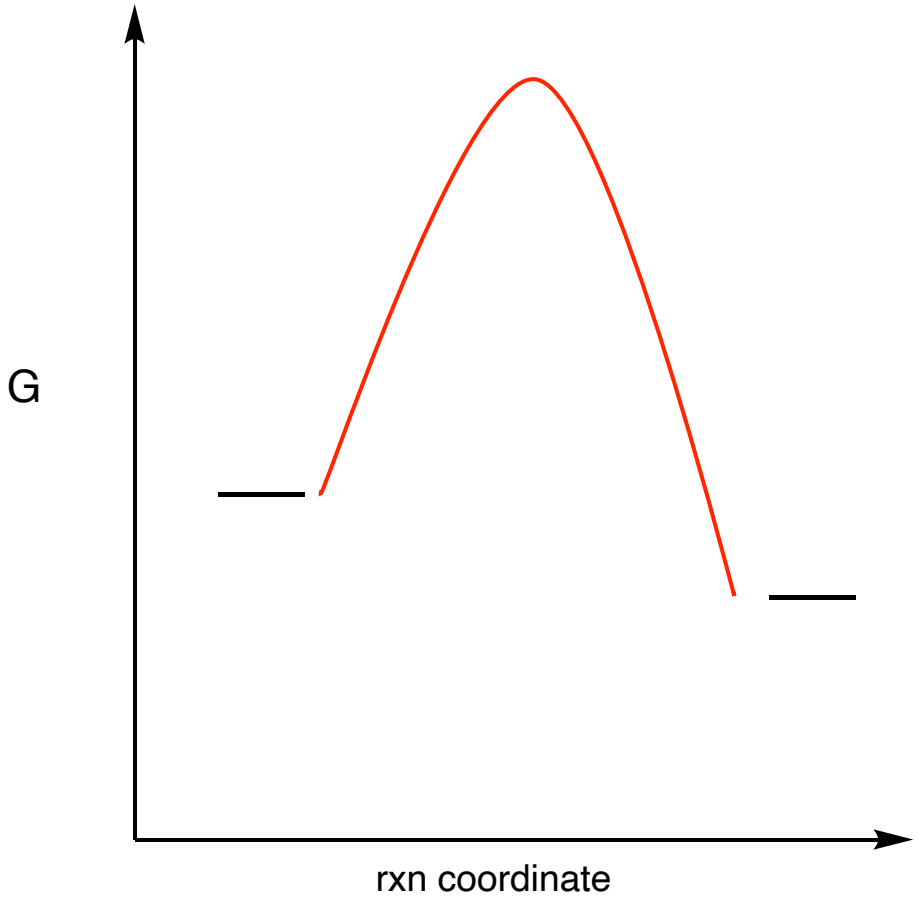
Factors Affecting S_N2 Reactions: The Leaving Group

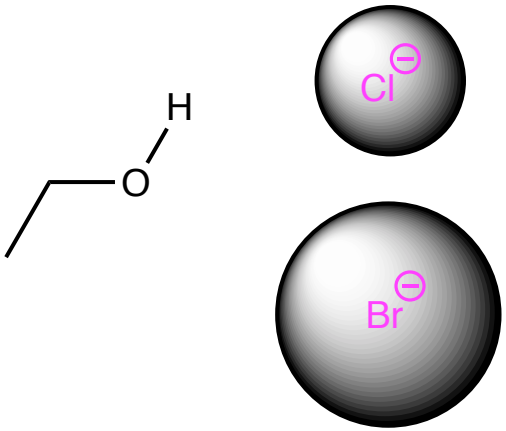


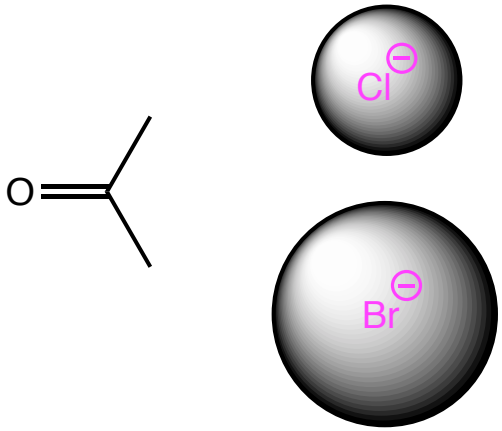


Relative reaction rates from Bruice, McMurry I^- : Br^- : Cl^- : F^- 30,000 : 10,000 : 200 : 1


HO⊖
H
C
Br
H
H
δ-
HO
H
C
δ-
Br
H H
‡
HO
H
C
H
H
Br⊖


G
rxn coordinate



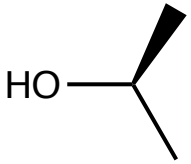


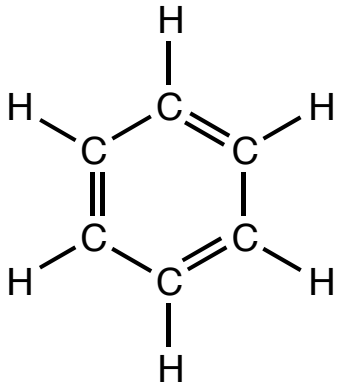
H—C≡CNa

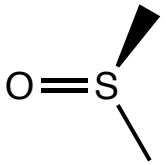
Protic or Aprotic Solvents

Practice

CH_3CH_2OH

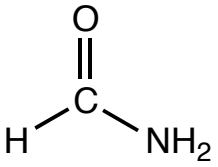


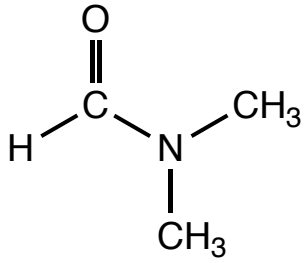


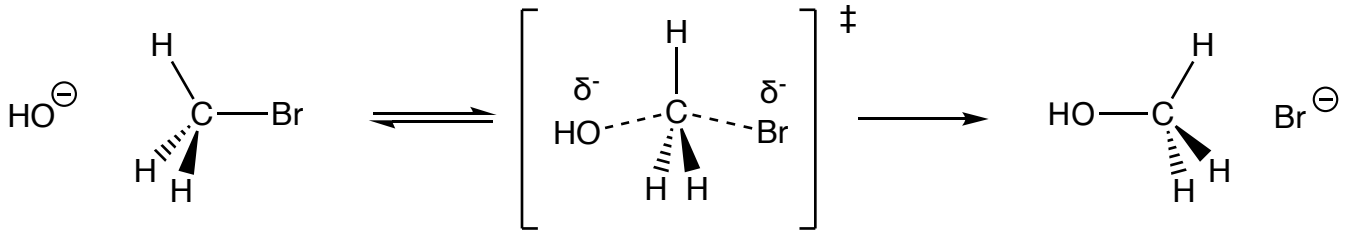


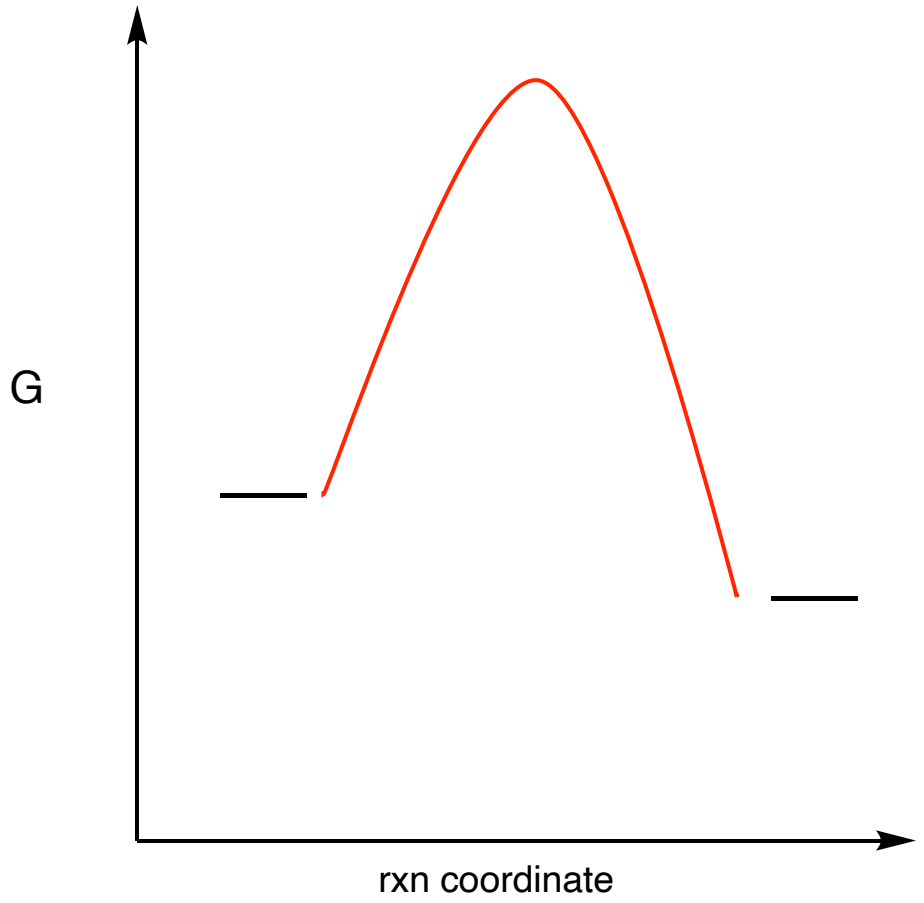
$CH_3CH_2OCH_2CH_3$

CH_2Cl_2






HO⊖
H
C
Br
H
H
δ-
δ-
HO
Br
H
H
H
‡
HO
C
H
H
Br⊖


G
rxn coordinate

Low degree of substitution on α-C and β-C atoms

Nu needs to be able to get to the α-C to react

Aprotic Solvents

Protic solvents weaken Nu's (stabilize Nu's via H-bonding like interaction)
Aprotic solvents increase the reactivity of nucleophiles

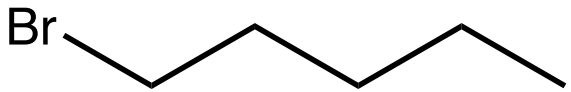
Good Leaving Group

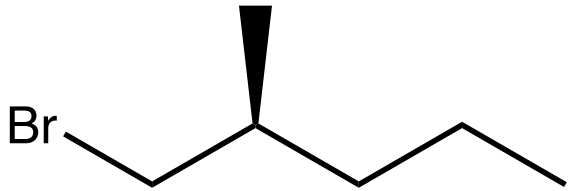
The more weakly basic the LG is, the easier it is for it to leave

Good Nucleophiles

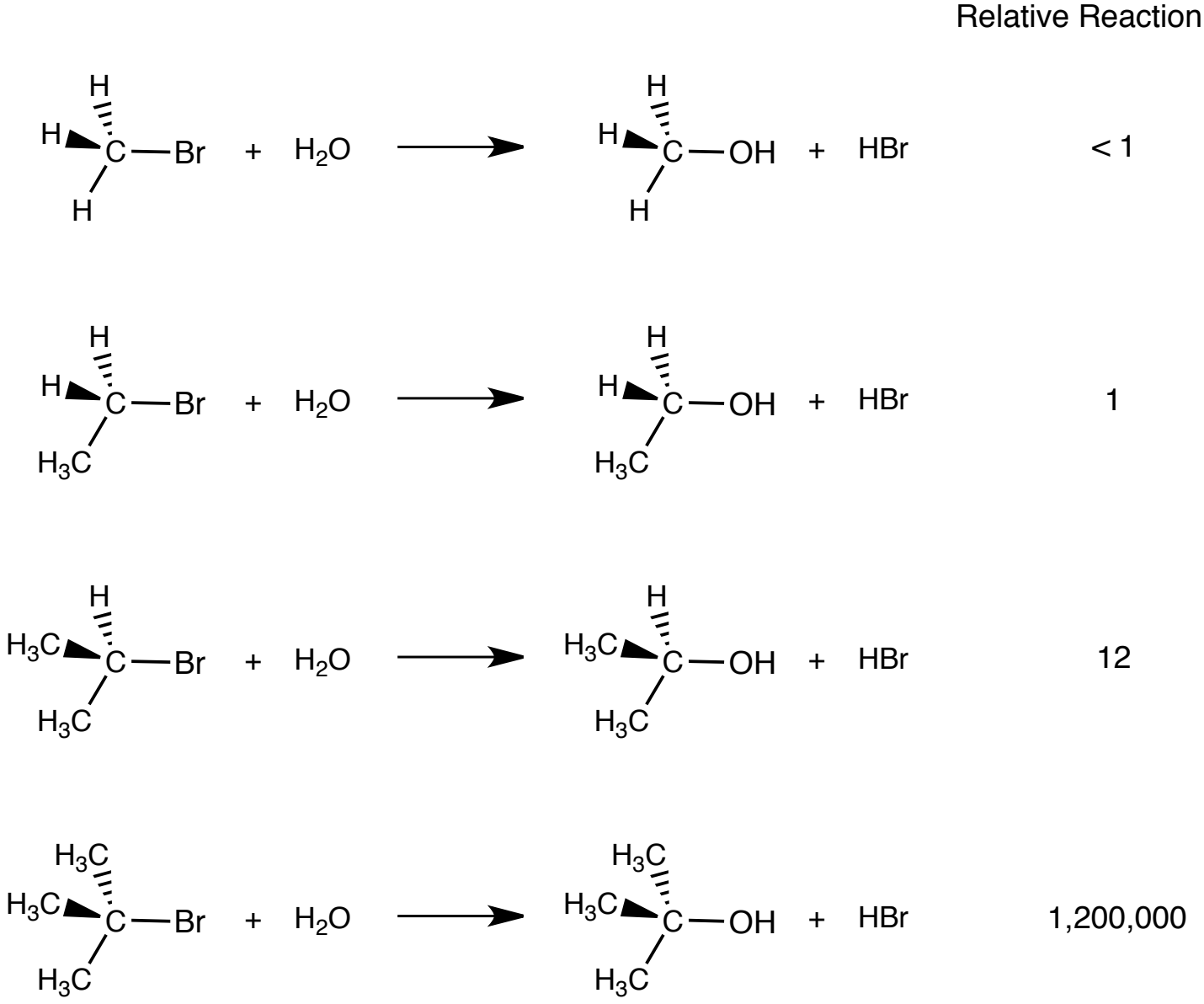
e^- rich, polarizable Nu's are best at initiating S_N2 reactions

α-C and β-C



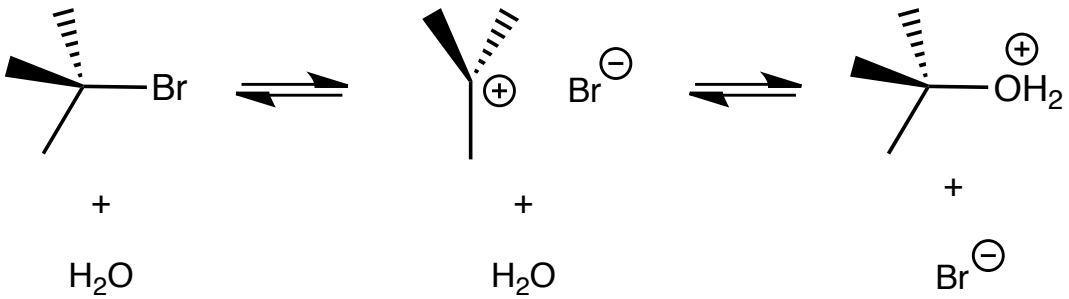


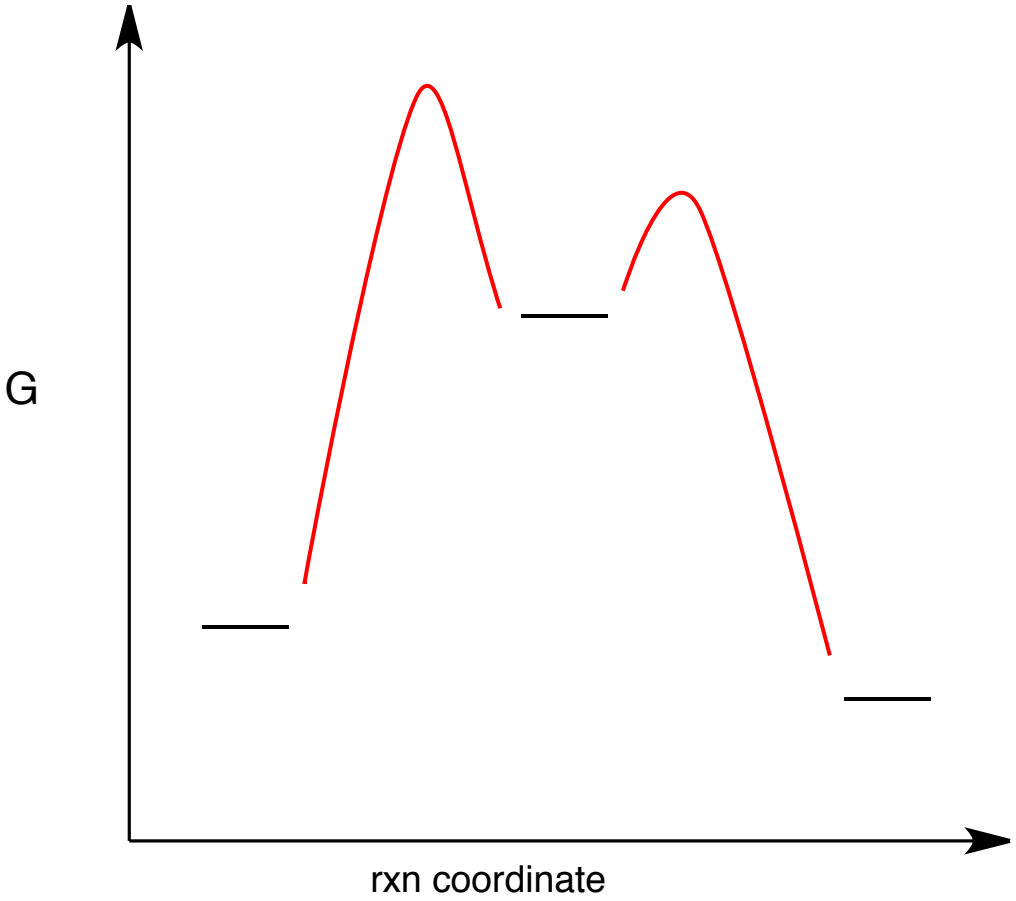
Rates of Hydrolysis of Alkyl Bromides

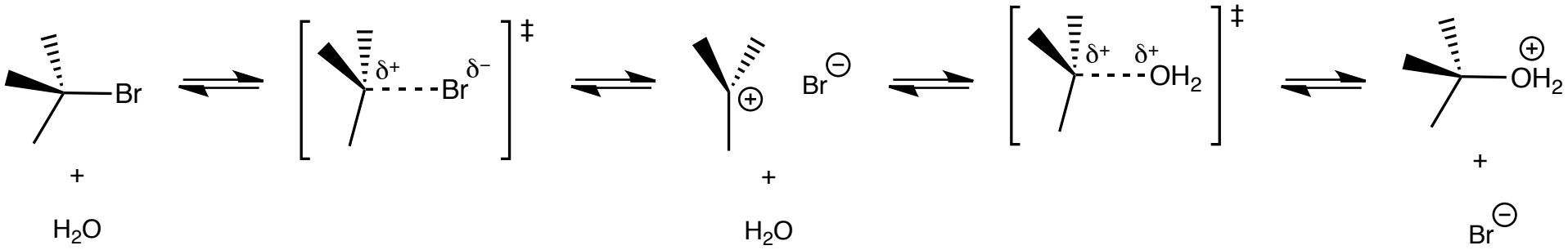


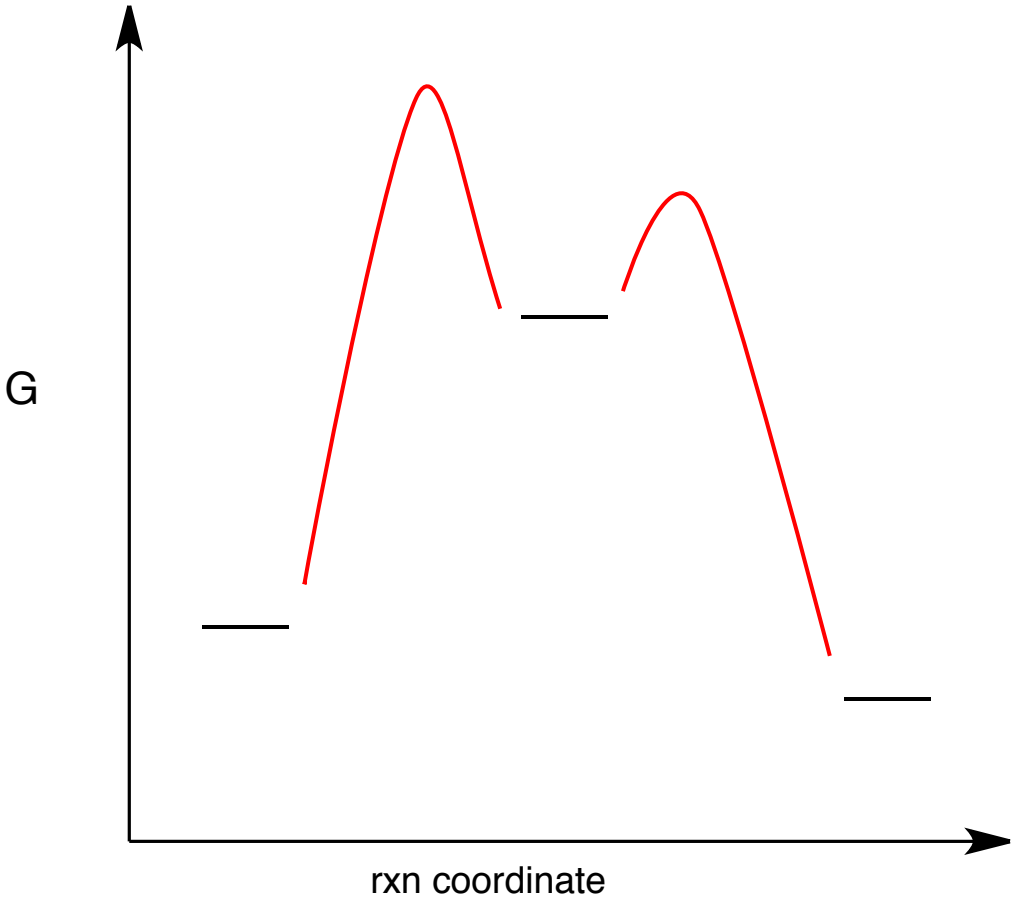
[1]Organic Chemistry, a 10th edition. McMurray, OpenStax

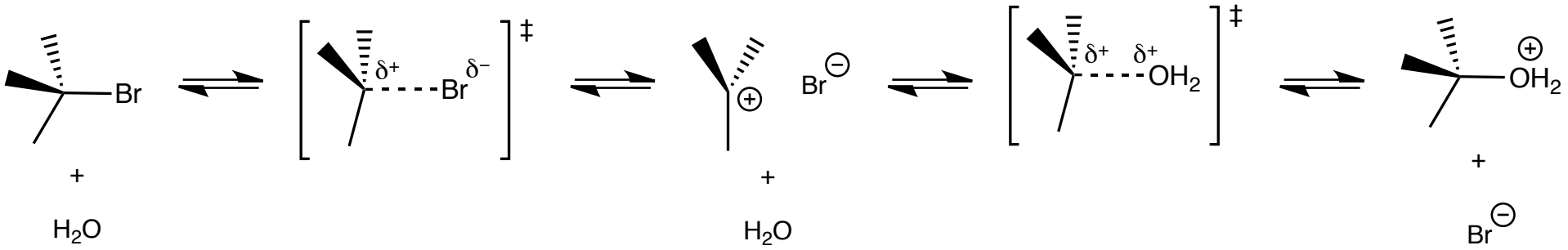
Factors Affecting S_N1: C^+ Stability

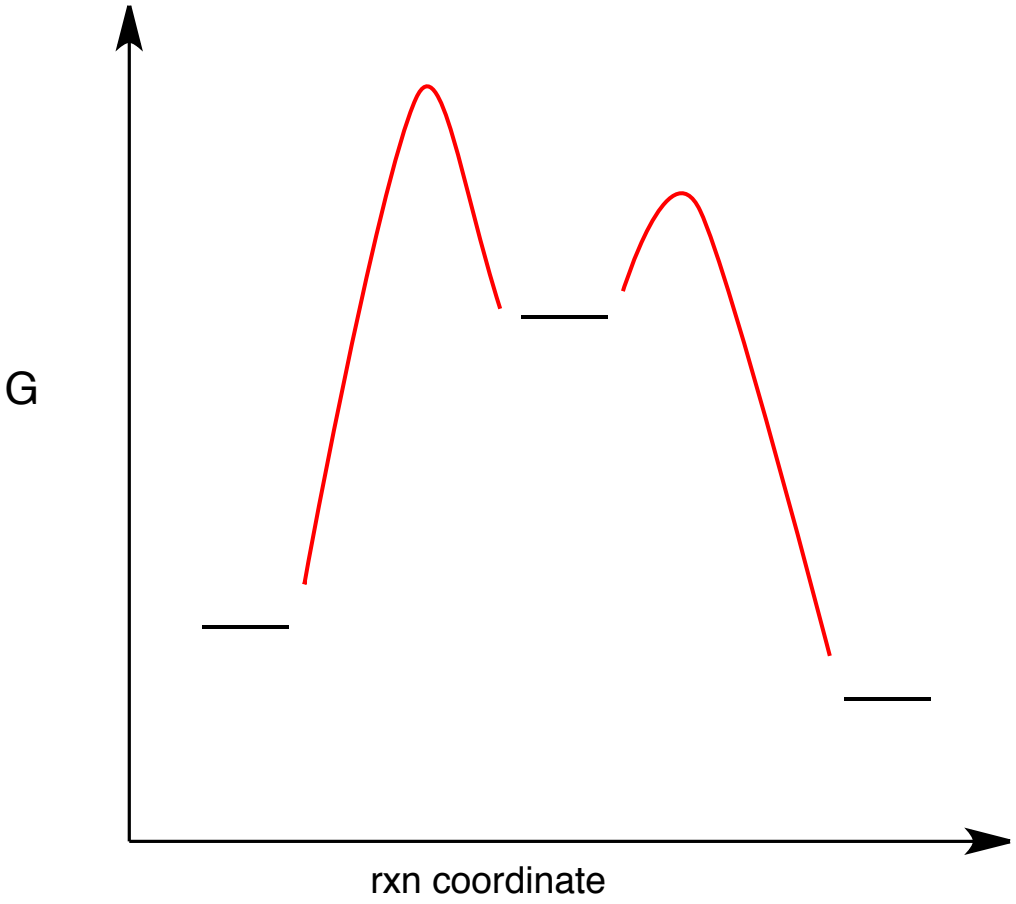


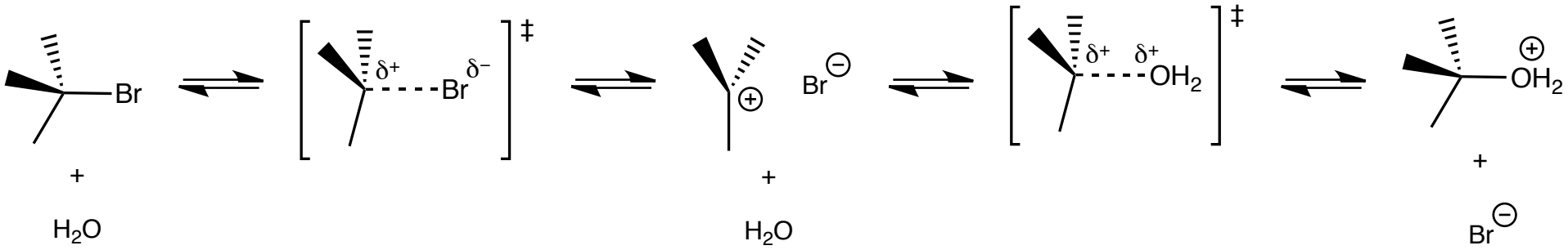


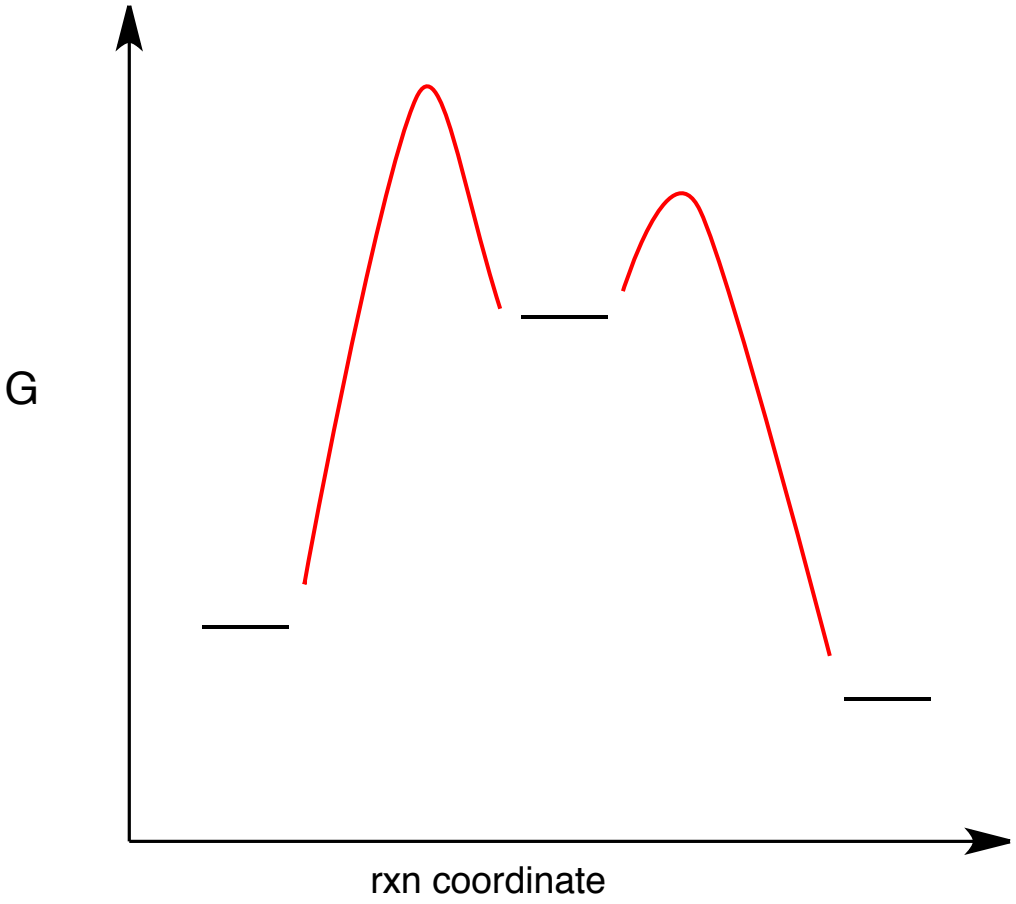

Br
δ+
δ−
Br
‡
Br
δ+
δ+
OH2
‡
OH2
+
H2O
+
H2O
+
Br


G
rxn coordinate


Br
δ+
δ−
Br
‡
Br
δ+
δ+
OH2
‡
OH2
+
H2O
+
H2O
+
Br


G
rxn coordinate


Br
δ+
δ−
Br
‡
Br
δ+
δ+
OH2
‡
OH2
+
H2O
+
H2O
+
Br


G
rxn coordinate

High degree of substitution on α-C or electron delocalization to promote C^+ stability

1° α-C < 2° α-C ~ 1° allylic ~ 1° benzylic < 3° α-C ~ 2° allylic ~ 2° benzylic < 3° allylic ~ 3° benzylic

Protic Solvents - encourage S_N1 mechanisms

Help stabilize transition state by stabilizing (–) charge that builds on LG as α-C to LG bond breaks

Good Leaving Group

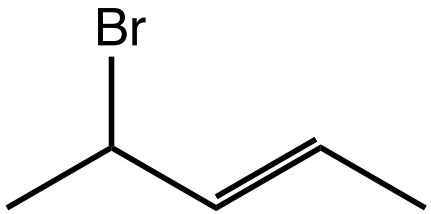
LG's that are low in energy (very weakly basic atoms/molecules) make forming the C^+ intermediate easier

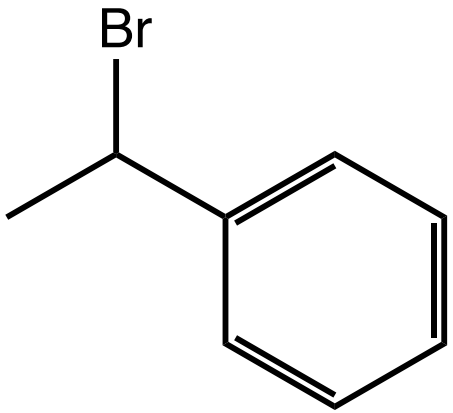
Weak Nucleophiles

Weak Nu's have to wait for C^+ to form to react…

Strongly basic Nu's cause side reactions on 2° and 3° α-C's

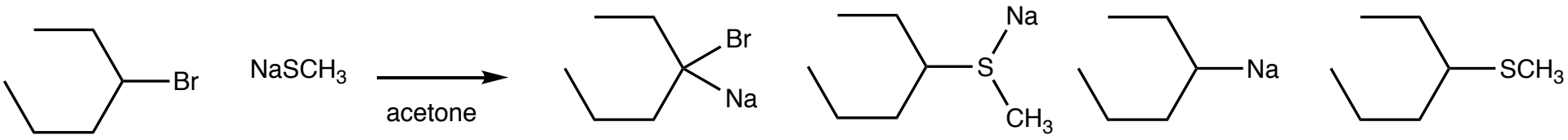
Allylic and Benzylic Positions





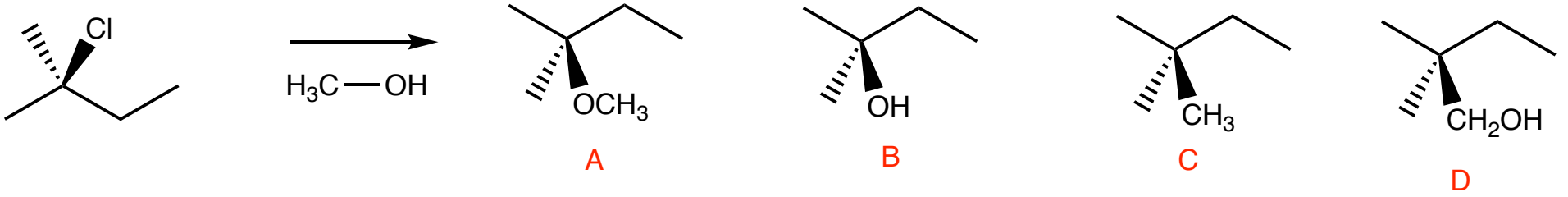
S_N2	**S_N1**
Two molecules collide in a 1 step mechanism	Dissociation of **one molecule** controls the rate of a two step reaction
bimolecular rate determining step	**unimolecular** rate determining step
stereochemistry is inverted	stereochemistry is a mixture of inverted and retained (not inverted)
methyl, 1°, 2°	3° alkyl 2° allylic/benzylic substrates
better the nucleophile the faster the reaction	the nucleophile is not involved in the rate determining step
good nucleophile	so so nucleophile
polar aprotic solvent	polar protic solvent

Reactions: S_N2 (ignoring stereochemistry)



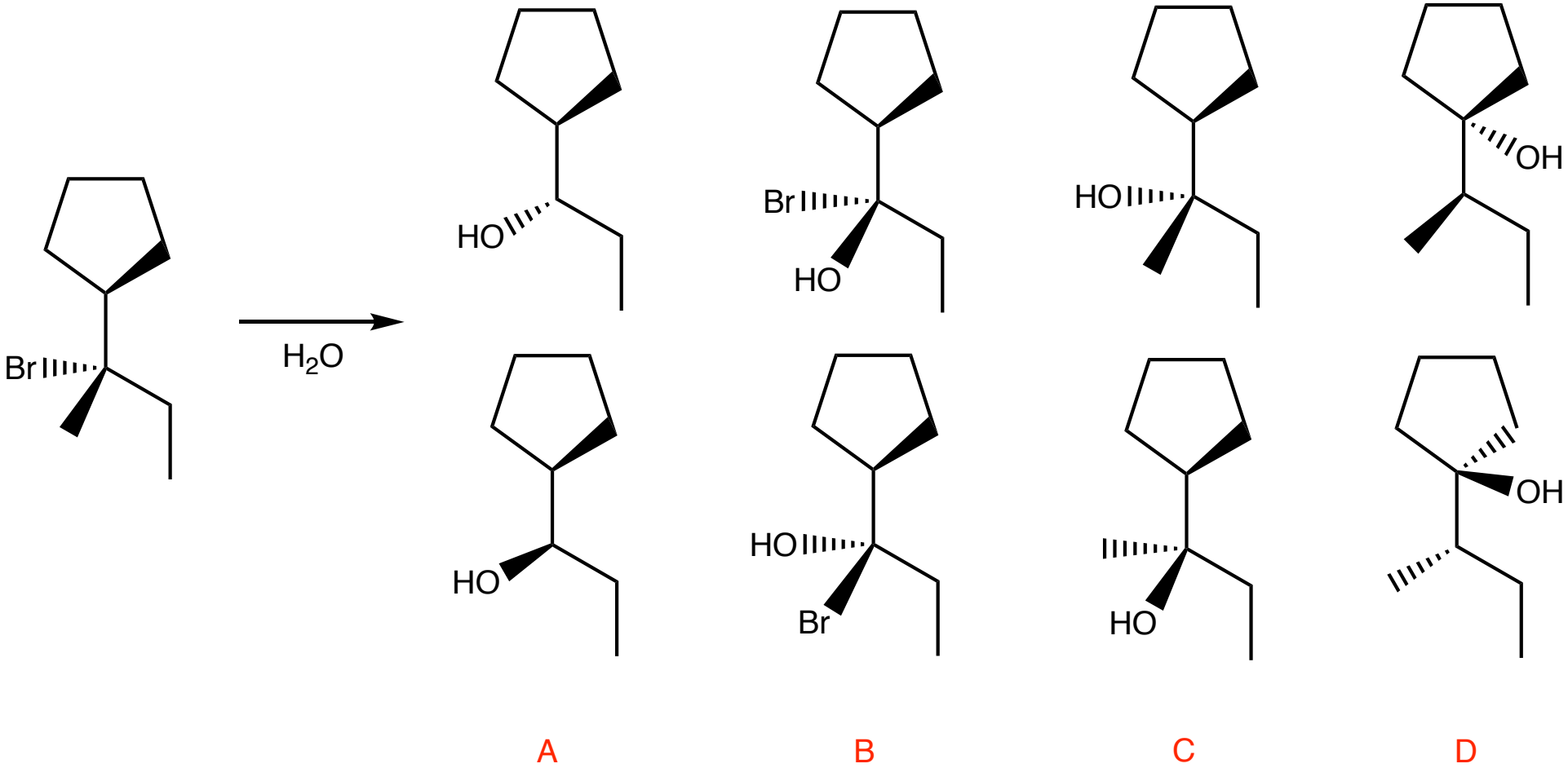
A B C D

Reactions: S_N1 (not ignoring stereochemistry)

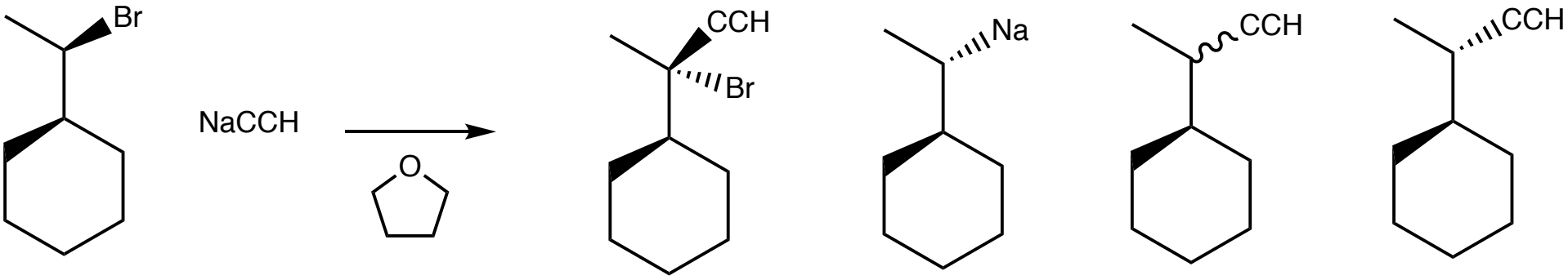


A B C D

Reactions: S_N? (not ignoring stereochemistry)



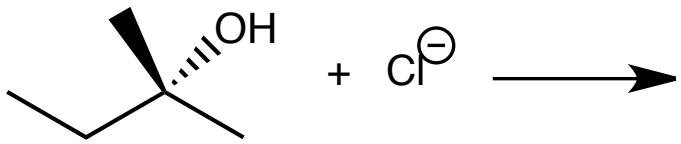
Reactions: S_N? (not ignoring stereochemistry)



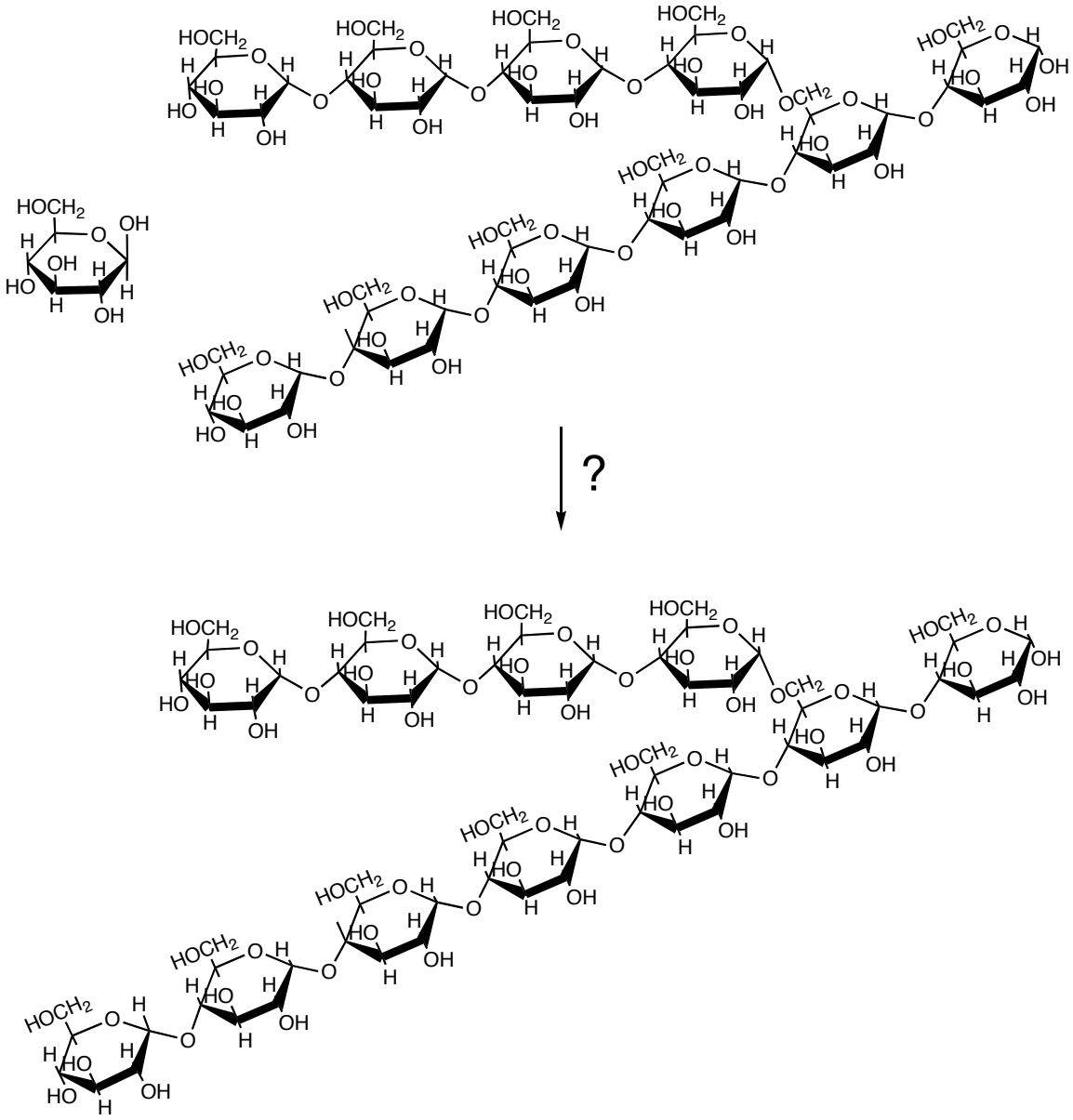
A B C D

Hydroxide is **not** a good leaving group

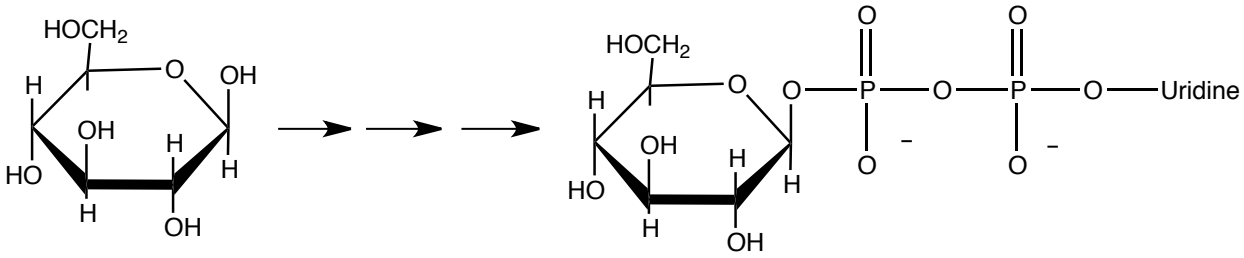
Sections 10.5 and 17.6



Why consider substitution reactions with alcohols?

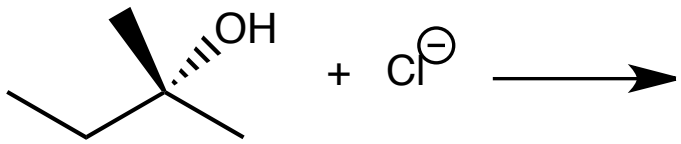


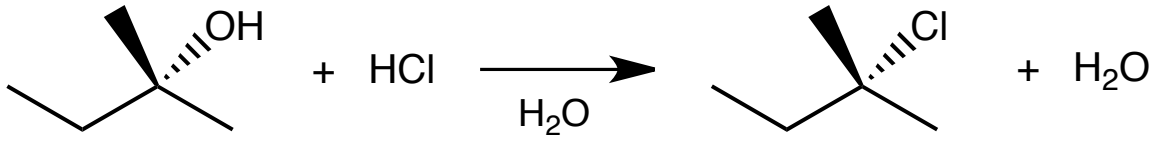
Biochemical Conversion of a Bad Hydroxyl Leaving Group to a Good Phosphate Leaving Group

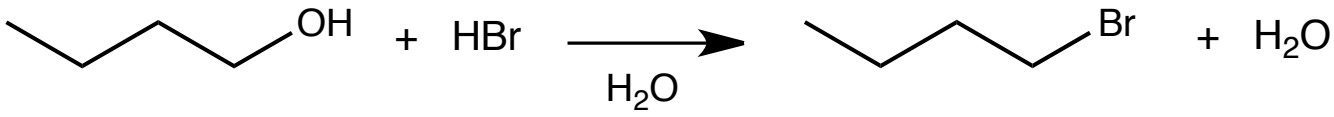


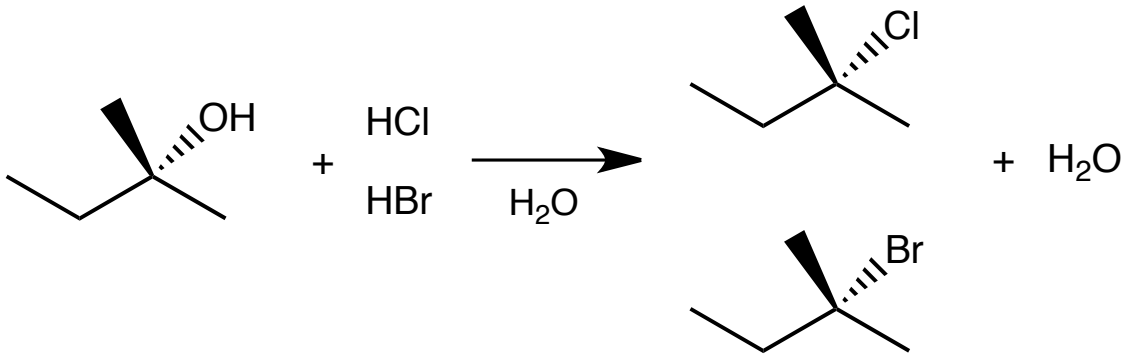
Hydroxide is **not** a good leaving group

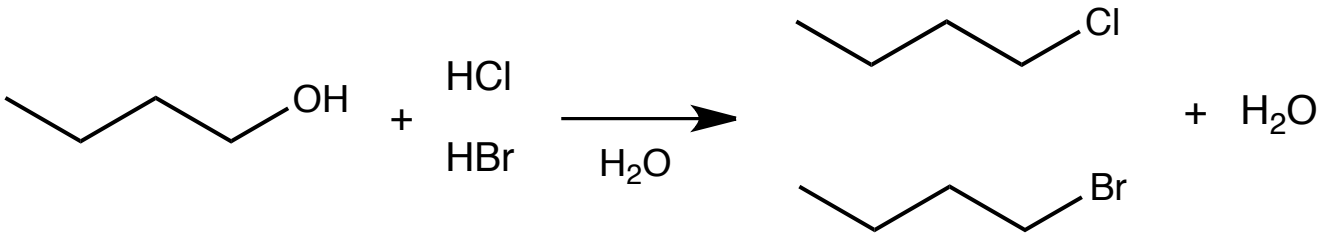
Sections 10.5 and 17.6




OH
+ HCl
H_2O
Cl
+ H_2O


OH
+ HBr
H_2O
Br
+ H_2O

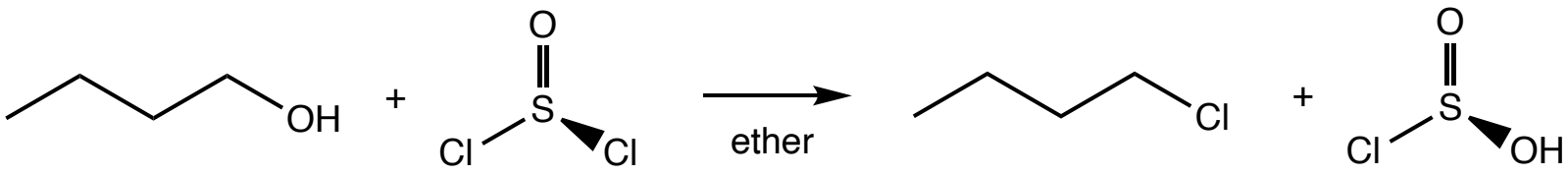




1-butanol reaction				t-butanol reaction			
area under 1-chlorobutane peak	area under 1-bromobutane peak	% Cl	% Br	area under t-butyl chloride peak	area under t-butyl bromide peak	% Cl	% Br
3.0184	39.1592	7.2	92.8	30.7310	89.2060	25.6	74.4
5.8862	91.6926	6.0	94.0	19.1382	61.8448	23.6	76.4
1.3768	21.3868	6.0	94.0	18.6189	41.2592	31.1	68.9
1.4171	19.5425	6.8	93.2	37.4692	81.1158	31.6	68.4

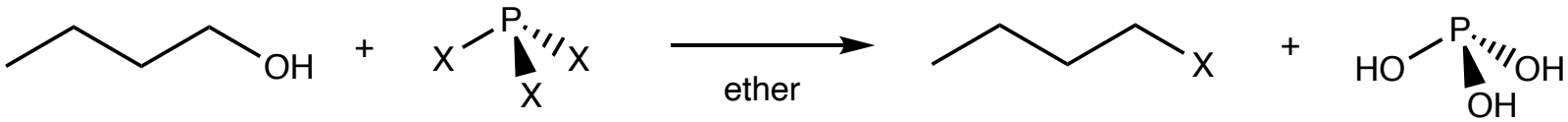
Other ways to convert OH^- to a good leaving group and do substitution using Lewis Acidic Atoms/Molecules

Sections 10.5 and 17.6



Other ways to convert OH^- to a good leaving group and do substitution using Lewis Acidic Atoms/Molecules

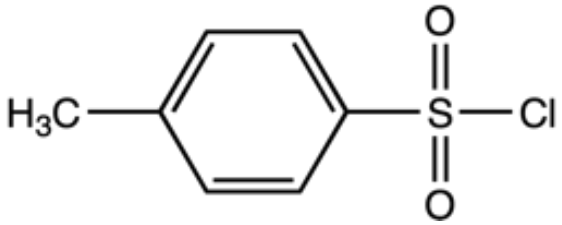
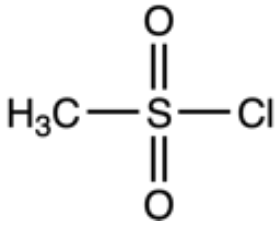
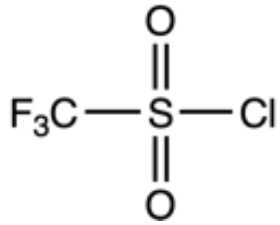
Sections 10.5 and 17.6



X = Cl or Br

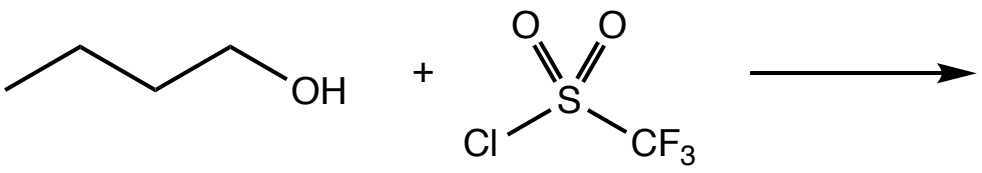
How about just making great leaving groups?

Sections 10.5 and 17.6

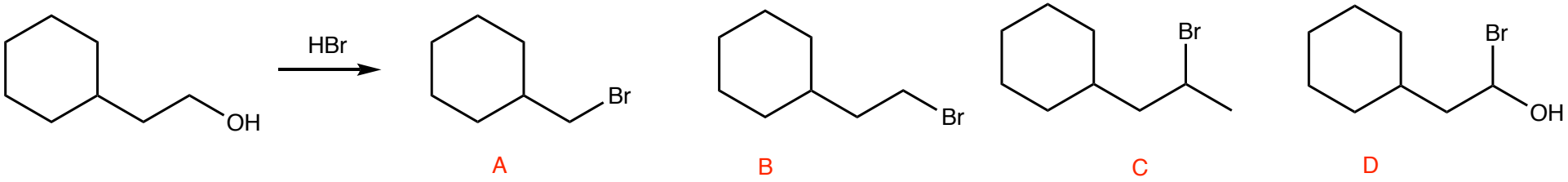
p-toluenesulfonylchloride	methanesulfonyl chloride	trifluoromethanesulfonyl chloride
		
p-toluenesulfonate a.k.a. toscylate	methanesulfonate	trifluoromethanesulfonate a.k.a. triflate

How about just making great leaving groups?

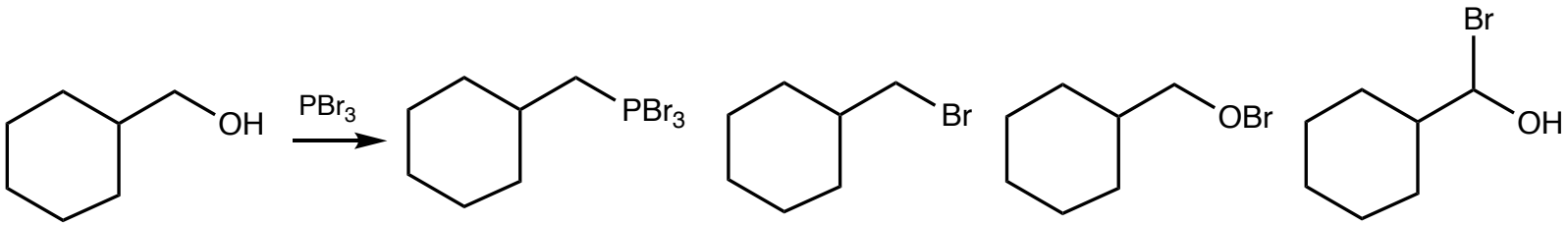
Sections 10.5 and 17.6



Reactions

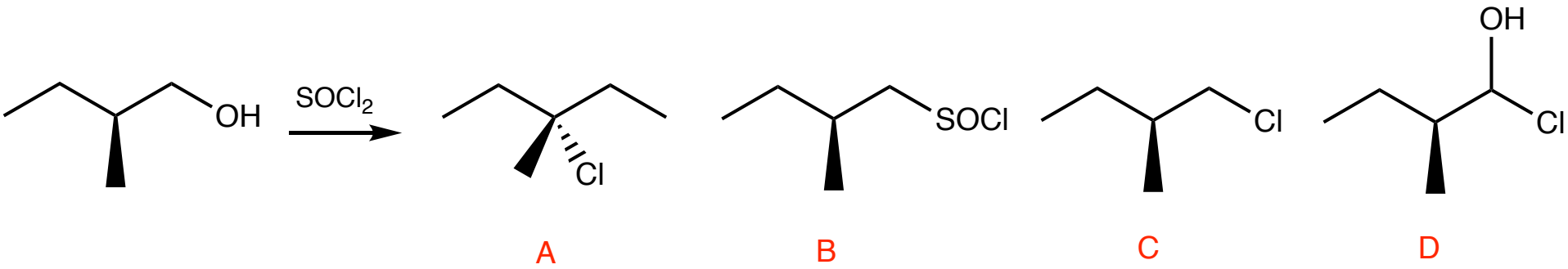


A B C D

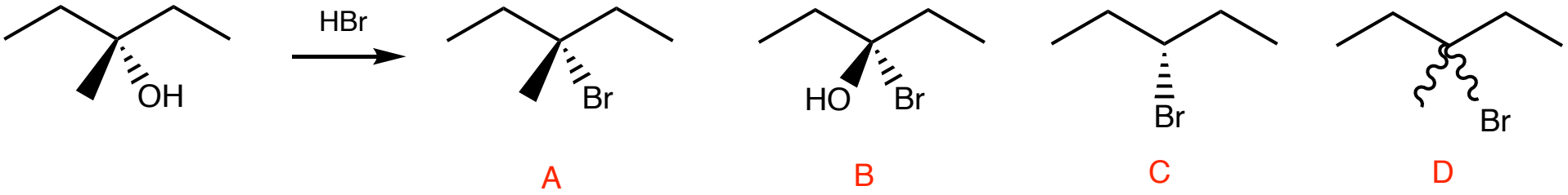


A B C D

Reactions

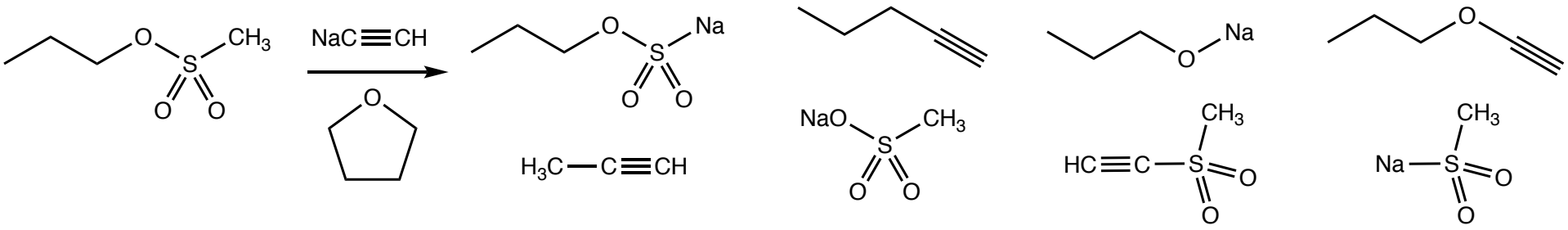


A B C D



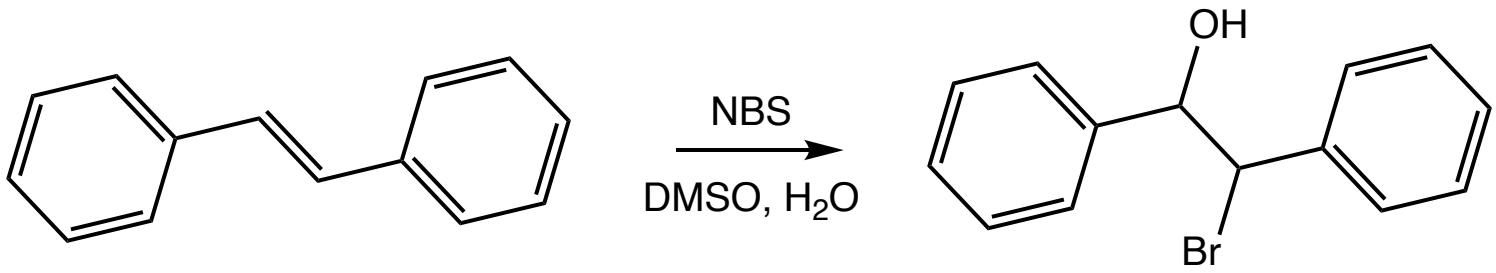
A B C D

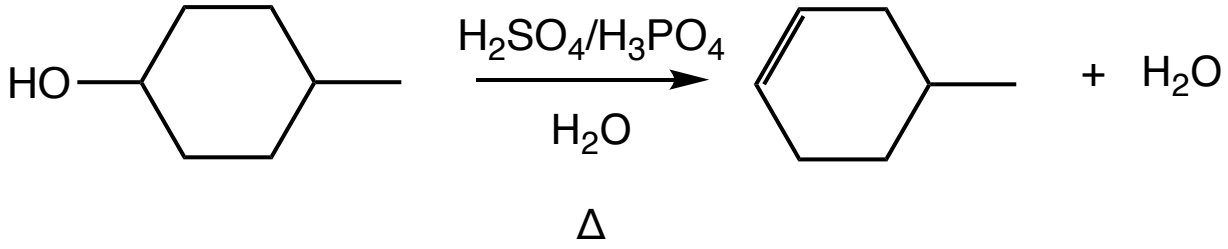
Reactions

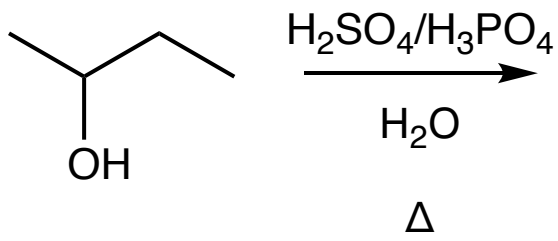


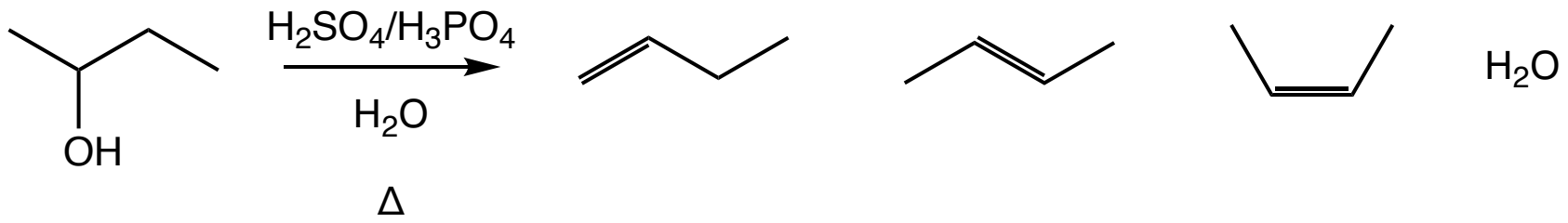
A B C D

E Add Stereoselectivity Lab

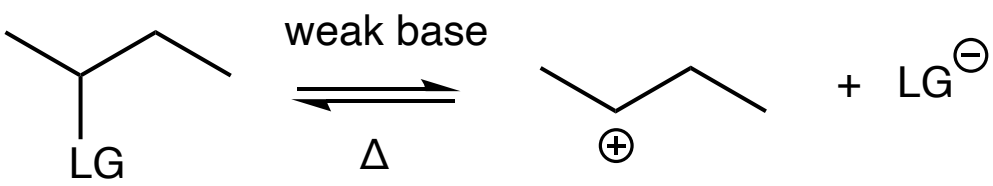


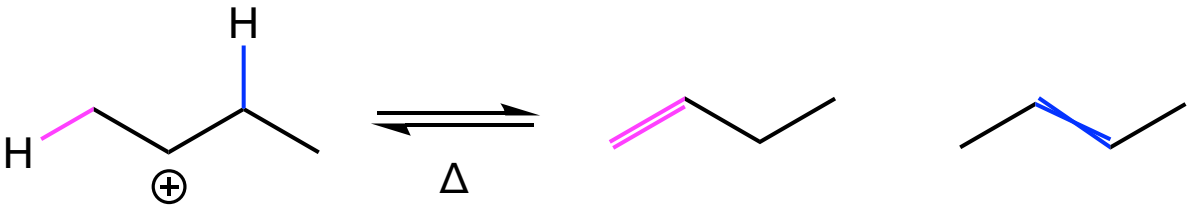

HO
H_2SO_4/H_3PO_4
H_2O
Δ
+ H_2O

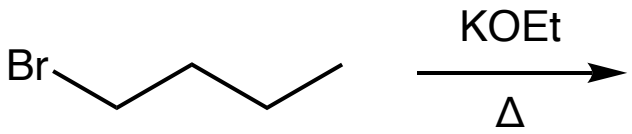

OH
H2SO4/H3PO4
H2O
Δ

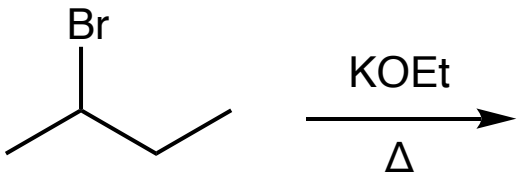


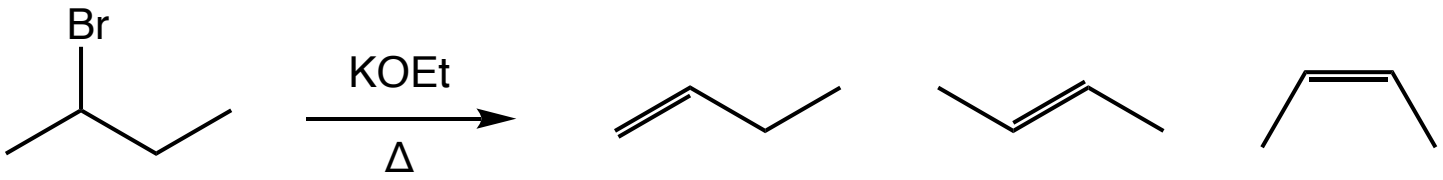
Section 7.6: Stability of Alkenes

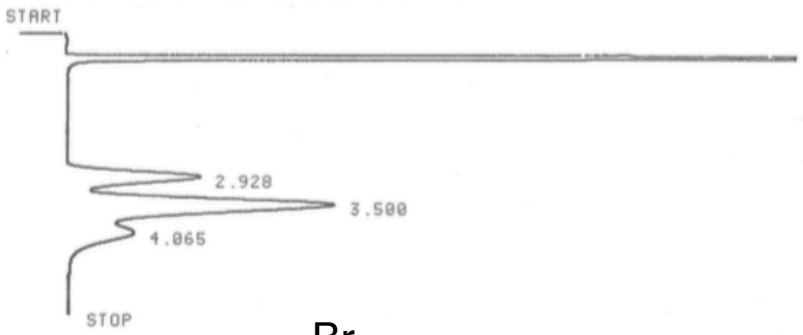

weak base
LG
Δ
+ LG⊖

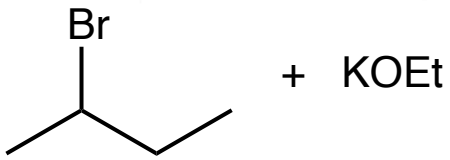

H
H
Δ


Br
KOEt
Δ

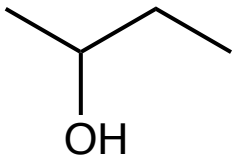

Br
KOEt
Δ



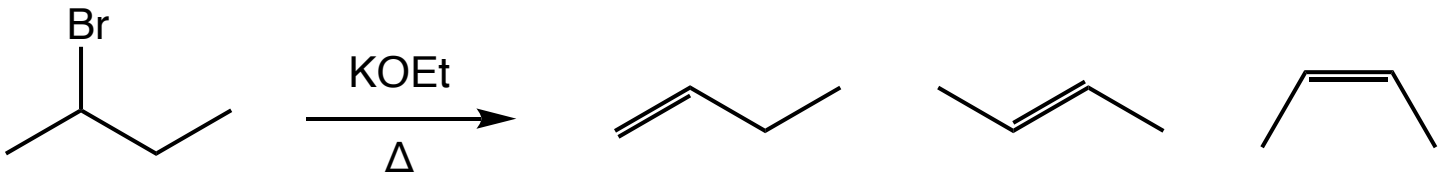


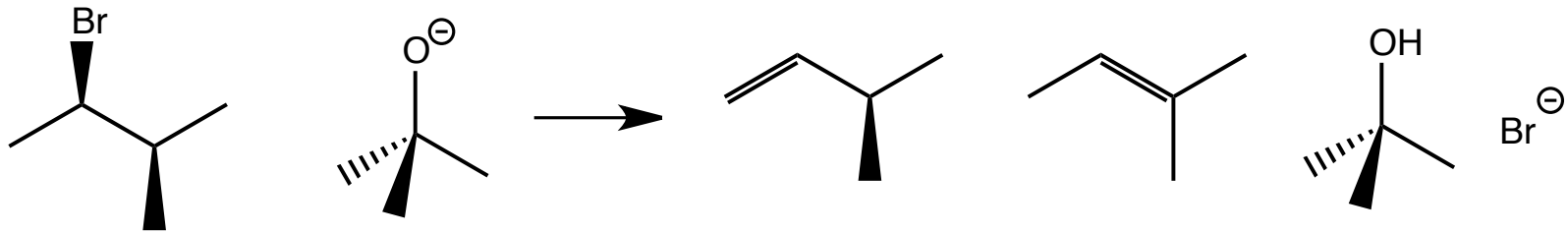


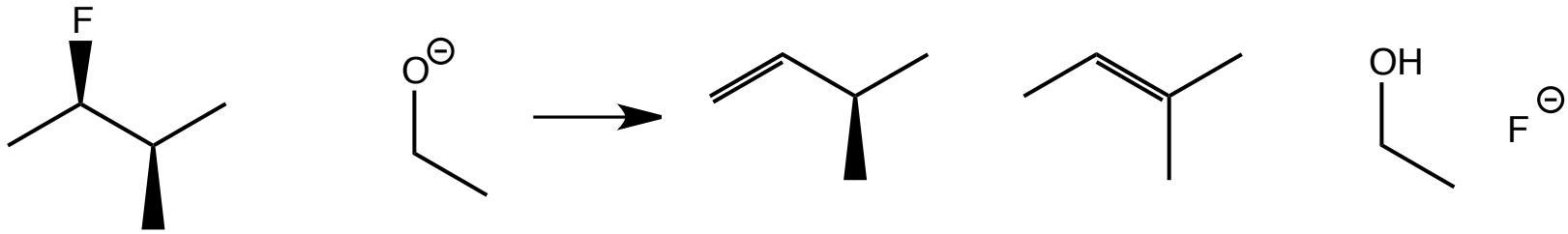
+ KOEt

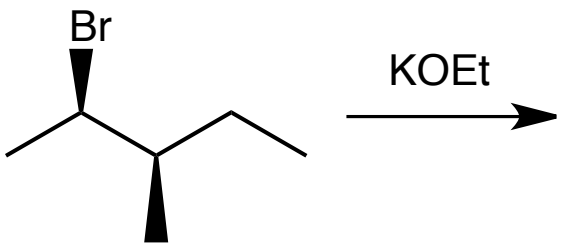


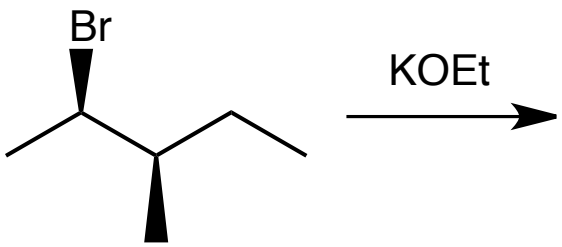
+ H_2SO_4/H_3PO_4 (aq)

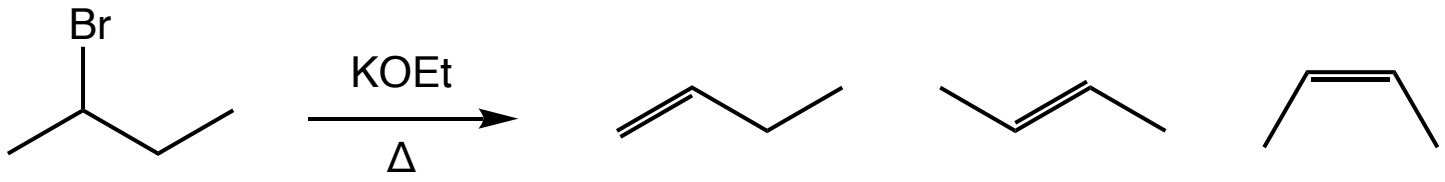

Br
KOEt
Δ

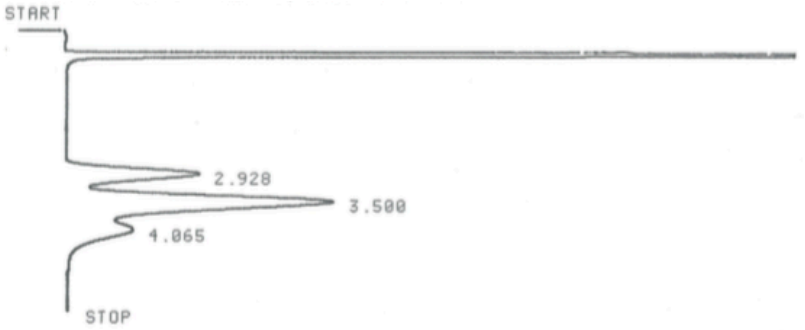

Br
O⊖
OH
Br⊖

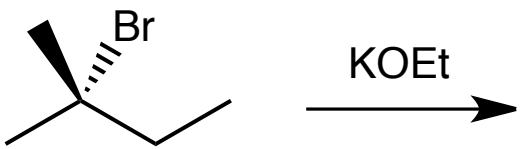

F
O
OH
F


Br
KOEt


Br
KOEt

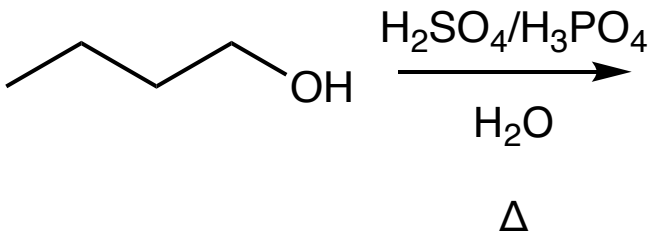

Br
KOEt
Δ

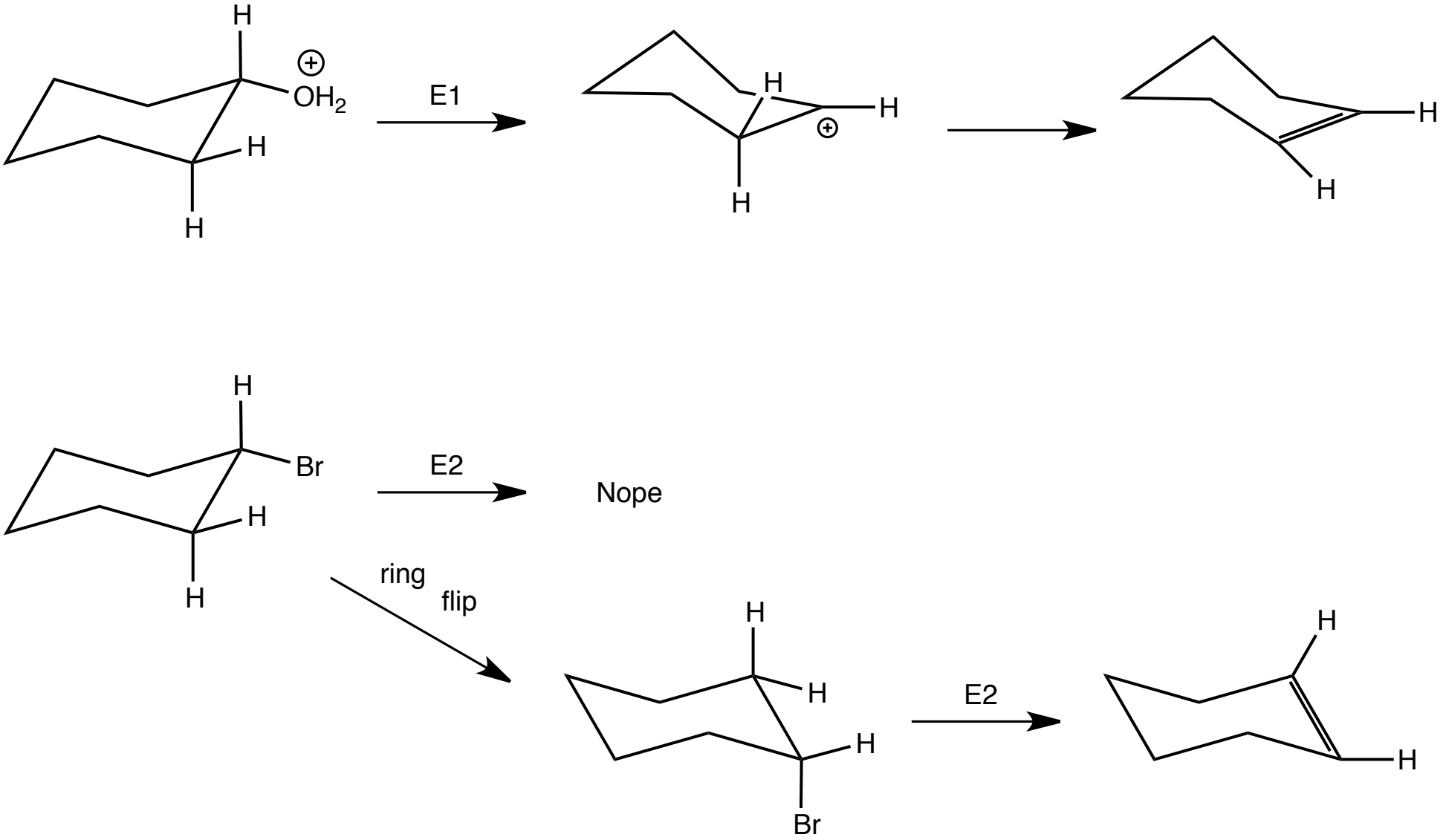

START
2.928
3.500
4.065
STOP


Br
KOEt

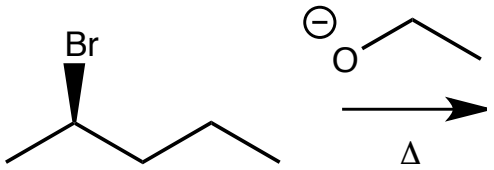
Elimination: Issues with Acid Catalyzed Elimination of Alcohols

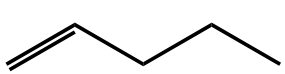
Sections 11.7 - 11.11 and 17.6



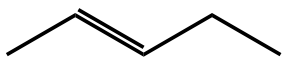

H
OH2
H
H
E1
H
H
H
H
H
Br
H
H
E2
Nope
ring
flip
H
H
H
Br
E2
H
H

Practice

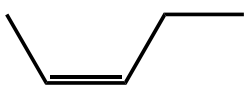




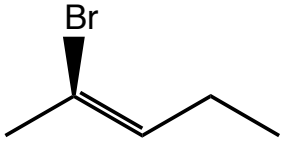
A



B



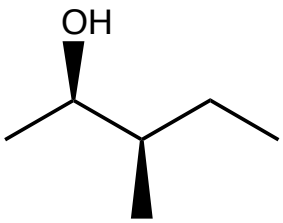
C



D

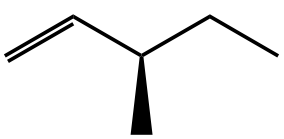
Elimination

Practice

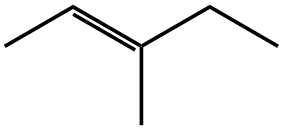


H_2SO_4/H_3PO_4

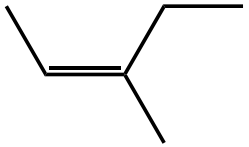
Δ



A



B



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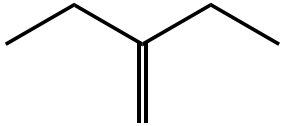
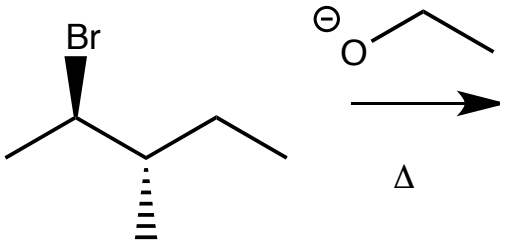
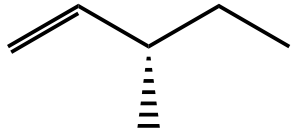


D

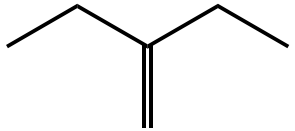
Elimination

Practice

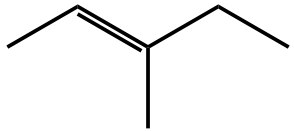




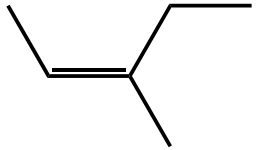
A



B



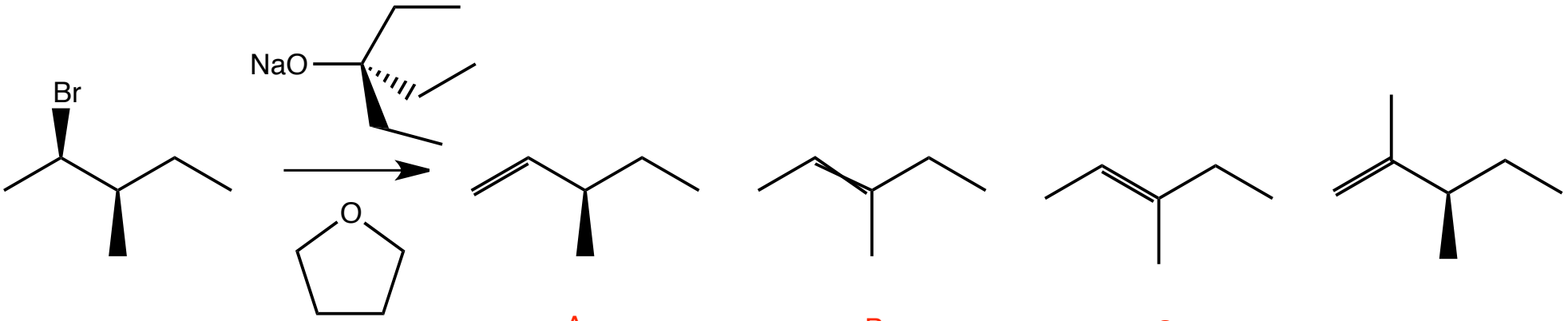
C



D

Elimination

Practice



A

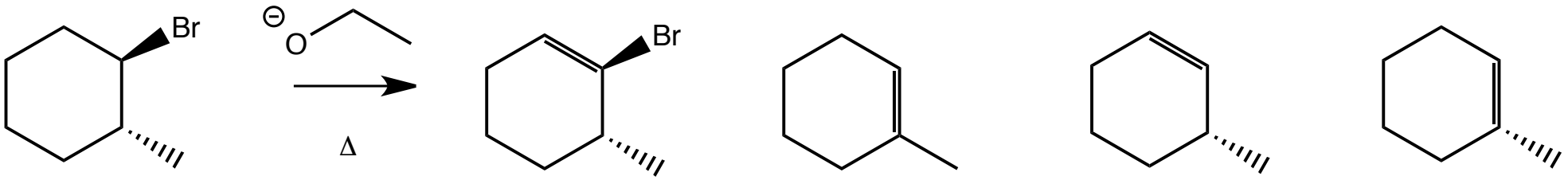
B

C

D

Elimination

Practice



A

B

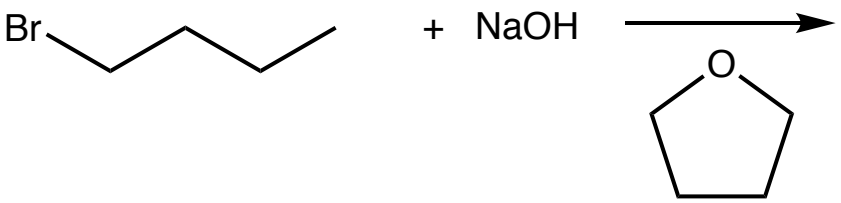
C

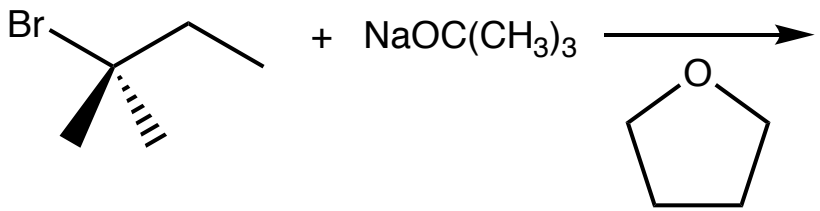
D

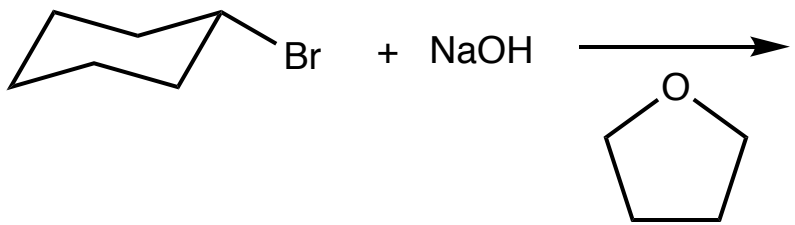
$S_N2/E2$ $S_N1/E1$

Conjugate Acid	pK_a	Nucleophile
HI	–10	I^-
HBr	–9	Br^-
HCl	–7	Cl^-
$CH_3OH_2^+$	–2.5	CH_3OH
H_3O^+	–1.7	HOH
HF	3.2	F^-
H_2S	7.0	HS^-
HC≡N	9.1	$C{\equiv}N^-$
NH_4^+	9.4	NH_3
CH_3CH_2SH	10.5	$CH_3CH_2S^-$
CH_3OH	15.5	CH_3O^-
HOH	15.7	HO^-
HCCH	25	HCC^-

Competition







Competition