University of Illinois
at Chicago
UIC

Lecture 17

Organic Chemistry 1

Professor Duncan Wardrop

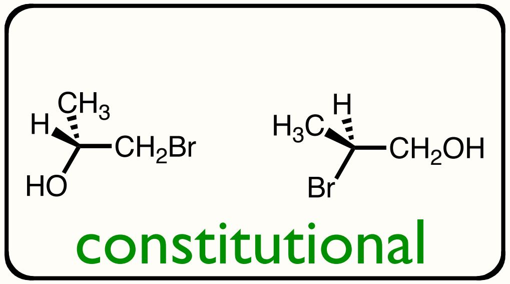
March 9, 2010

Chapter 8
Nucleophilic Substitution

Sections 8.1 - 8.7

Self-Test Question

Which pair of molecules are *diastereomers*?
Caution: meso forms are achiral; they are not stereoisomers.

A


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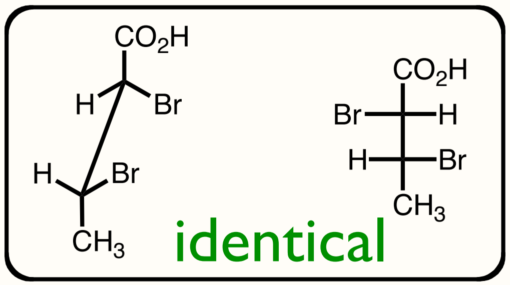

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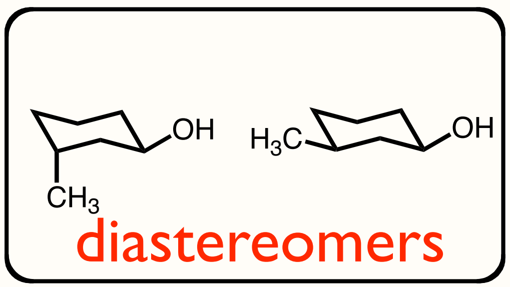

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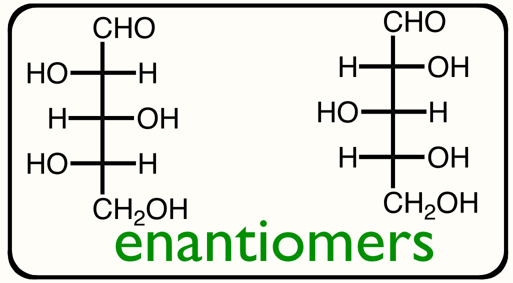

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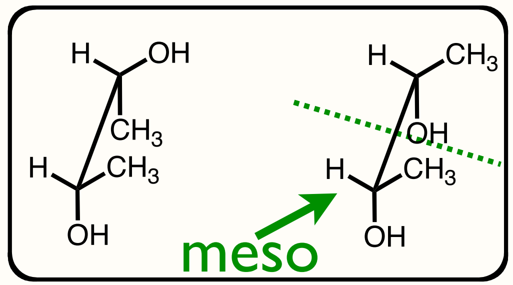
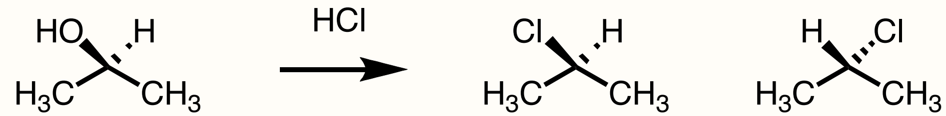


Self-Test Question

Which reaction below is *stereospecific*?

A


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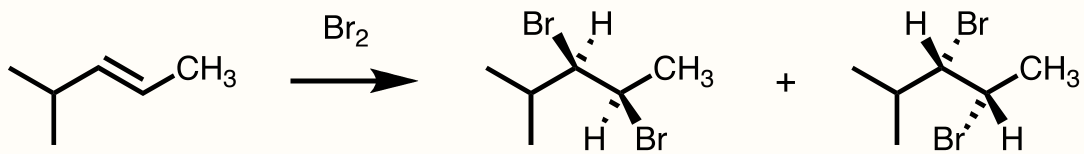

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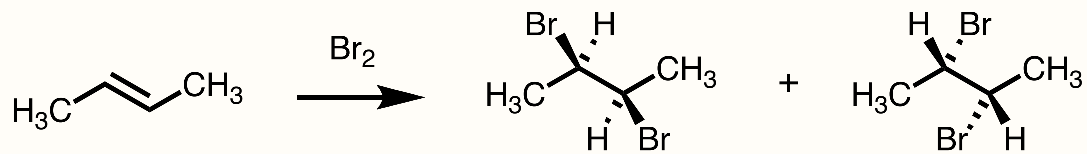

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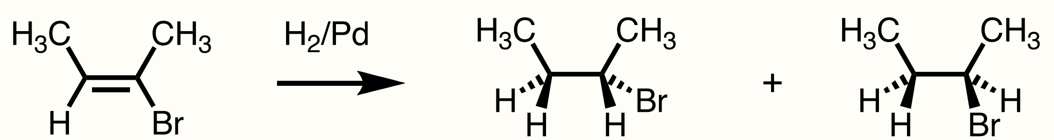


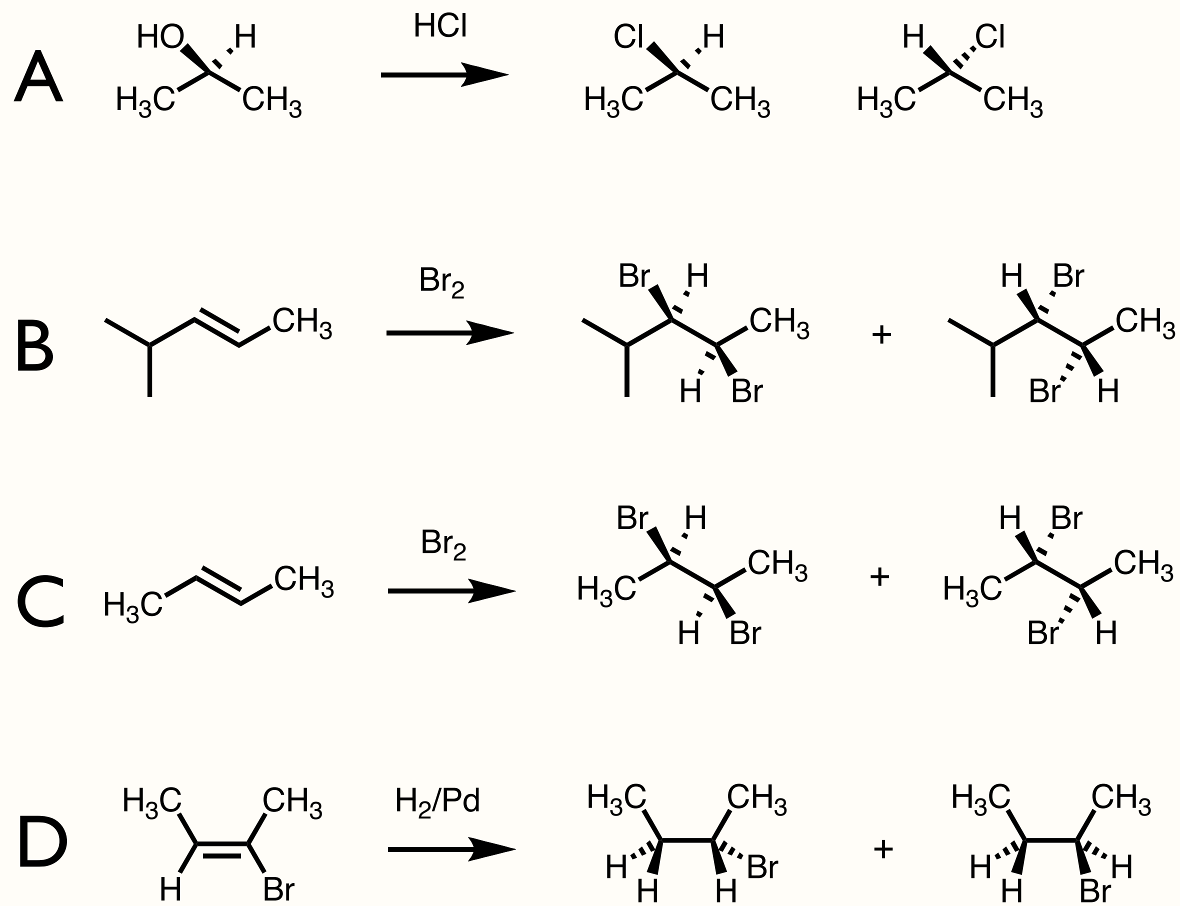
1. Are ≥2 configurational stereoisomers of the reactant <u>possible</u>?

no = can't be stereospecific

yes = go to next question

Self-Test Question

Which reaction below is *stereospecific*?



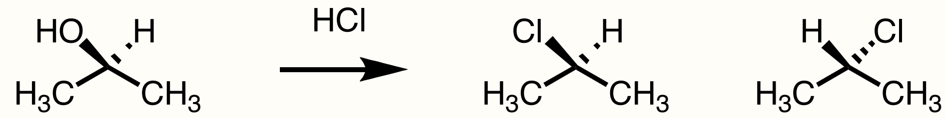
2. Are the <u>possible</u> products configurational stereoisomers ?

no = can't be stereospecific

yes = go to next question

Self-Test Question

Which reaction below is *stereospecific*?

A


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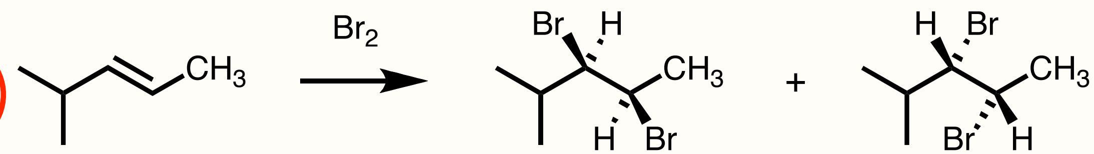
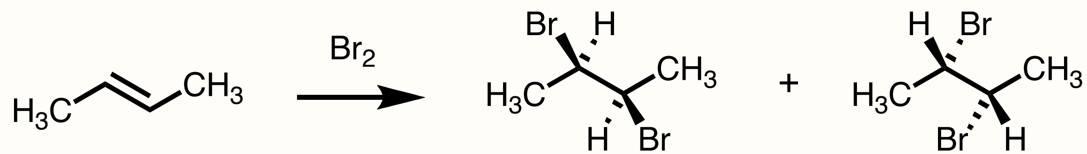


3. Are the products of each configurational reactant stereoisomers of each other ?

no = can't be stereospecific

yes = go to next question

C


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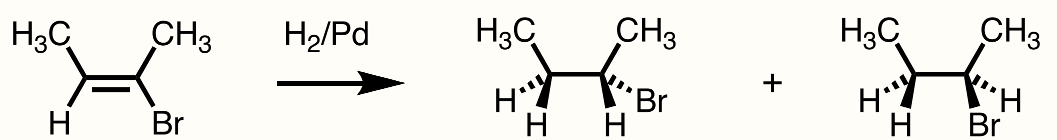

Self-Test Question

1. Are ≥2 configurational stereoisomers of the reactant <u>possible</u>?

no = can't be stereospecific

yes = go to next question √

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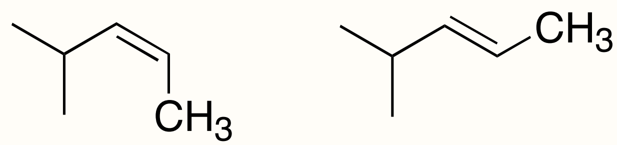
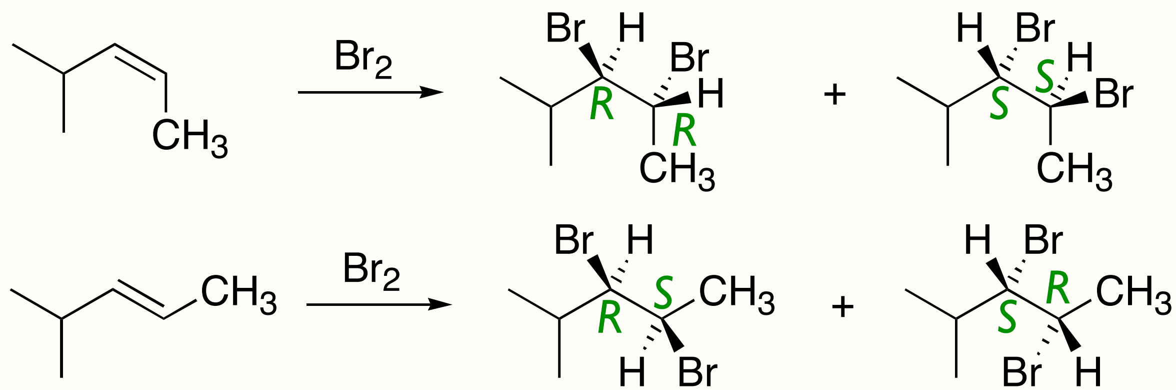


cis *trans*



RR + *SS*

diastereomers

RS + *SR*

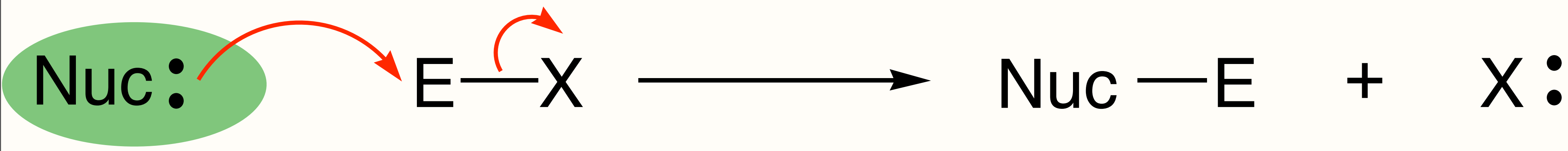
Nucleophilic Substitution

Nucleophiles Add to Electrophiles

$$\text{Nuc}\!: \quad \text{E}\!-\!\text{X} \longrightarrow \text{Nuc}\!-\!\text{E} \quad + \quad \text{X}\!:$$

Nucleophilic Substitution

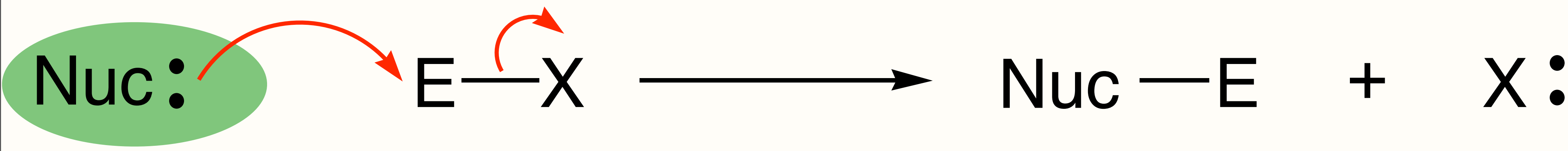
Nucleophiles Add to Electrophiles

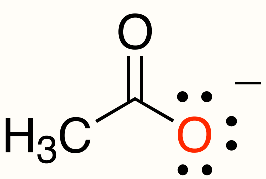


- nucleophiles are Lewis bases
- they contain pairs of electrons (usually lone pairs, but not always)
- donate electron pairs to form covalent bonds with electrophiles
- not all Lewis bases form covalent bonds

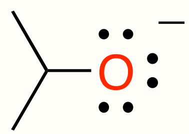
Anionic Nucleophiles

Nucleophiles Add to Electrophiles

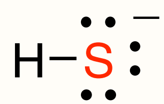




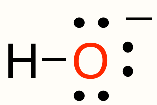
carboxylate



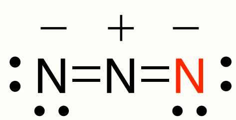
alkoxide



hydrogen sulfide



hydroxide



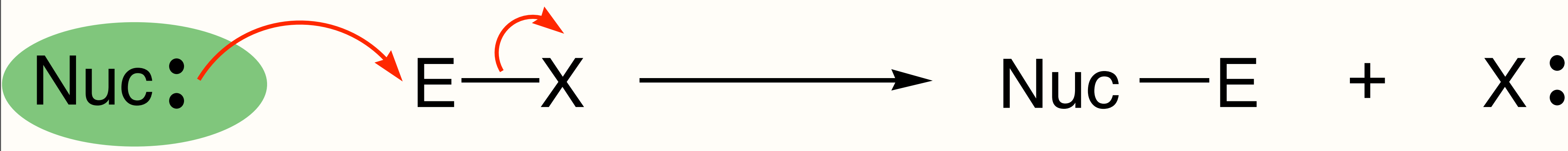
azide

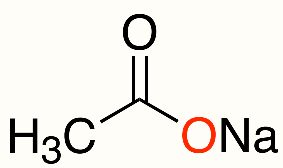
cyanide

- many nucleophiles are anionic (negative charge)
- nulceophilic atom (one forming new bond) highlighted in red

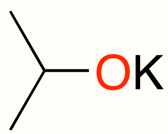
Anionic Nucleophiles

Nucleophiles Add to Electrophiles





carboxylate

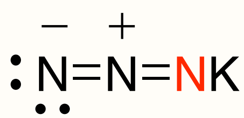


alkoxide

hydrogen sulfide

anionic nucleophiles are often used/written as their metal salts

hydroxide

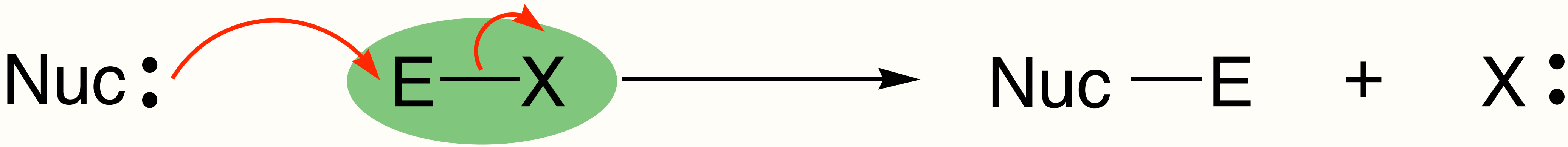


azide

cyanide

Alkyl Halide Electrophiles

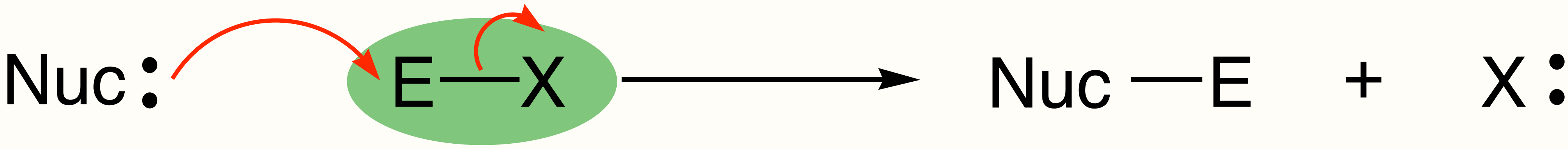
Nucleophiles Add to Electrophiles

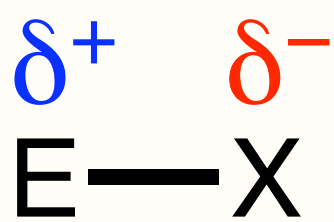


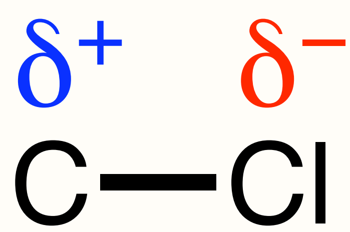
- electrophiles are Lewis acids
- accept electron pairs to form <u>covalent bonds</u> with nucleophiles
- usually contain a polar covalent bond where one atom is a good leaving group
- not all Lewis acids form covalent bonds

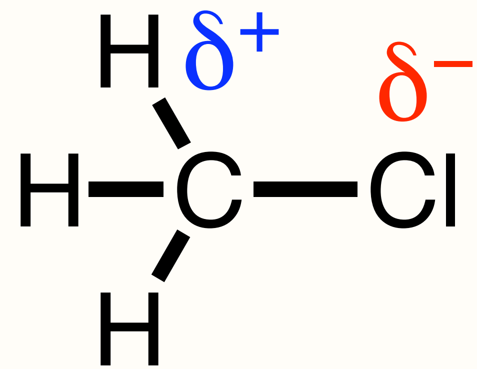
Alkyl Halides are Electrophiles

Nucleophiles Add to Electrophiles









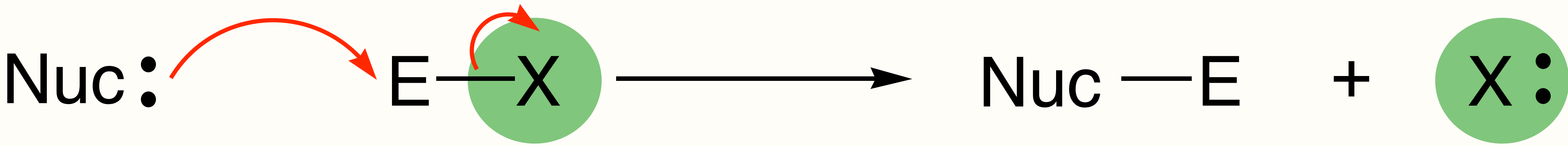
polar covalent bond when X is strongly electronegative

carbon-halogen bonds are polar covalent

alkyl halides are electrophiles; C of C-X bond, specifically

Leaving Groups

Nucleophiles Add to Electrophiles

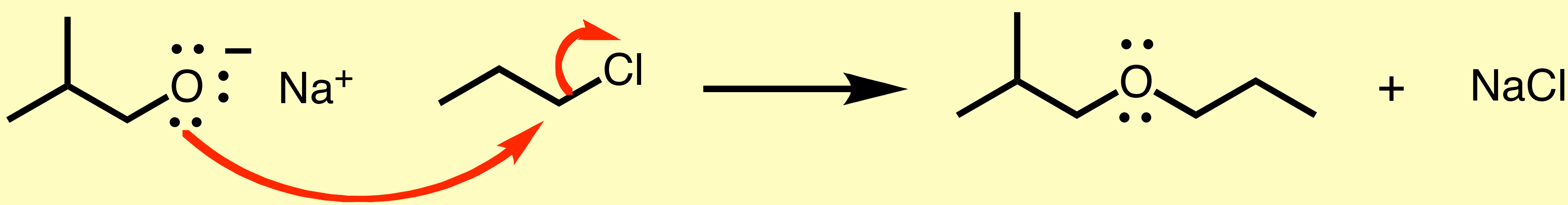


- atom losing a bond is called a leaving group (LG)
- typically a weak base; negative charge stabilized by electronegativity and/or resonance
- for exergonic reaction, the Nuc–E bond is stronger than E–X bond

Williamson Ether Synthesis

Nucleophiles Add to Electrophiles

$$\mathrm{Nuc}{:} \quad \mathrm{E}{-}\mathrm{X} \longrightarrow \mathrm{Nuc}{-}\mathrm{E} + \mathrm{X}{:}$$



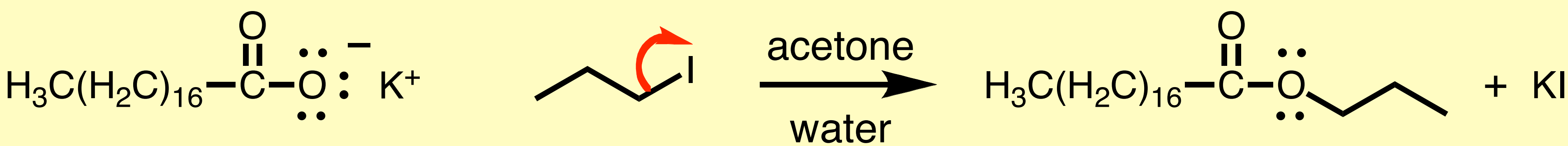
alkoxide alkyl halide ether

Williamson Ether Synthesis

Examples of Nucleophilic Substitution

Nucleophiles Add to Electrophiles

$$\text{Nuc:} \;+\; \text{E—X} \longrightarrow \text{Nuc—E} \;+\; \text{X:}$$



carboxylate

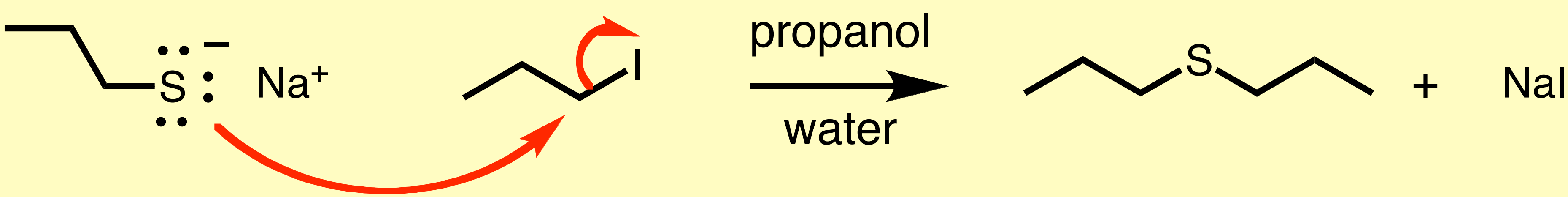
alkyl halide

ester

Examples of Nucleophilic Substitution

Nucleophiles Add to Electrophiles

Nuc: E—X ⟶ Nuc—E + X:



thiolate

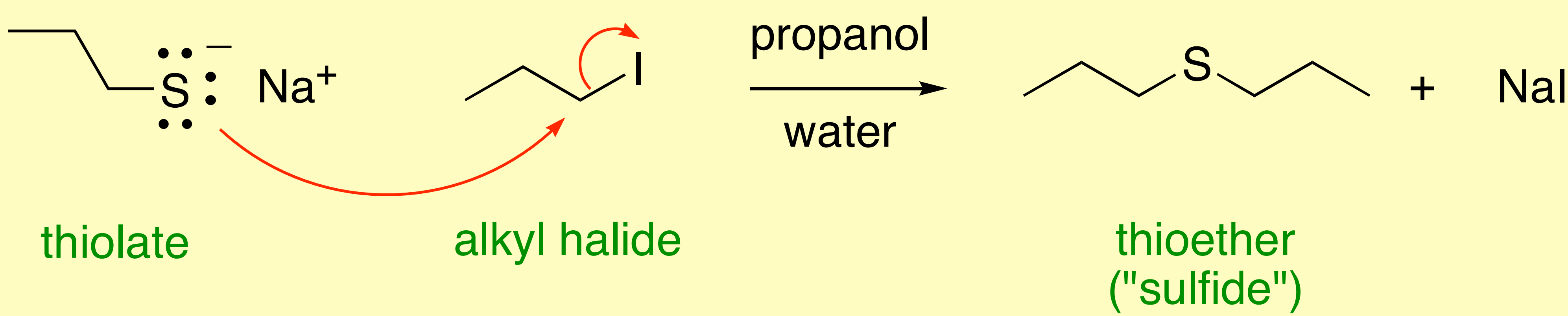
alkyl halide

thioether
(alkyl sulfide)

Examples of Nucleophilic Substitution

Nucleophiles Add to Electrophiles

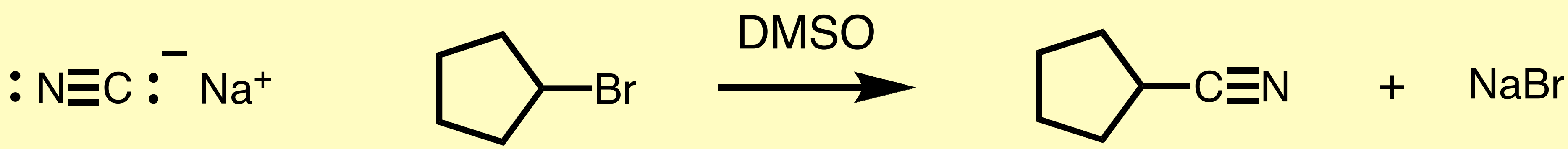
$$\text{Nuc:}\ \ \text{E}{-}\text{X} \longrightarrow \text{Nuc}{-}\text{E} \ + \ \text{X:}$$



Examples of Nucleophilic Substitution

Nucleophiles Add to Electrophiles

$$\mathrm{Nuc}\colon \quad \mathrm{E{-}X} \longrightarrow \mathrm{Nuc{-}E} + \mathrm{X}\colon$$



cyanide

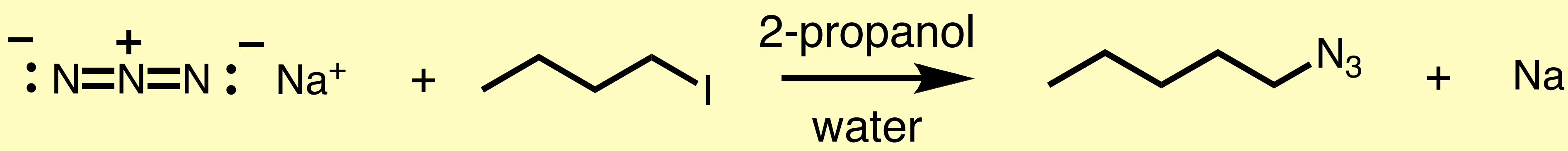
alkyl halide

nitrile
(alkyl cyanide)

Examples of Nucleophilic Substitution

Nucleophiles Add to Electrophiles

$$\text{Nuc:} \quad \text{E—X} \longrightarrow \text{Nuc—E} \quad + \quad \text{X:}$$



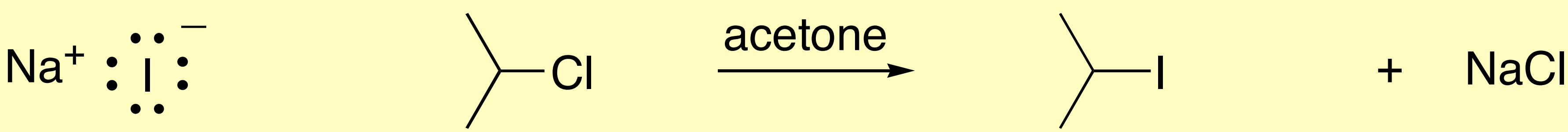
azide

alkyl halide

alkyl azide

Examples of Nucleophilic Substitution

Nucleophiles Add to Electrophiles

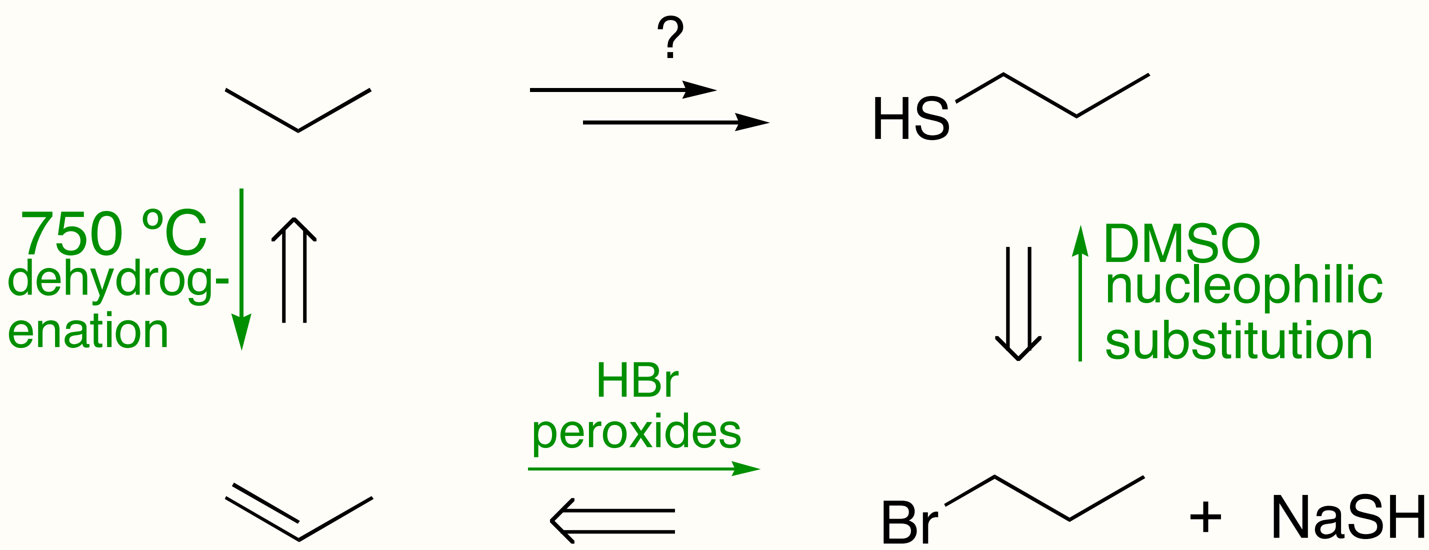


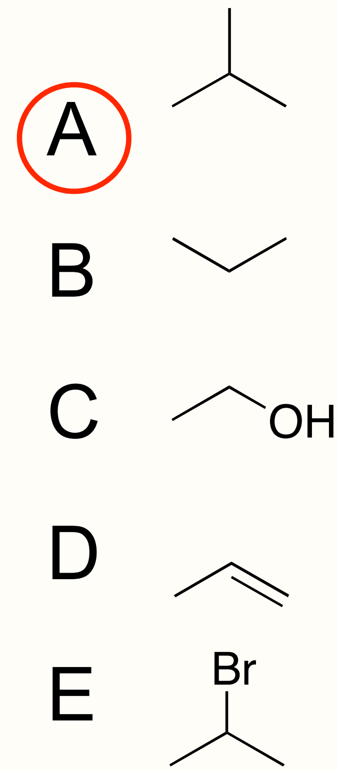
sodium iodide (sol in acetone) | alkyl halide | alkyl halide | sodium iodide (insol in acetone)

Finkelstein Reaction

Self Test Question

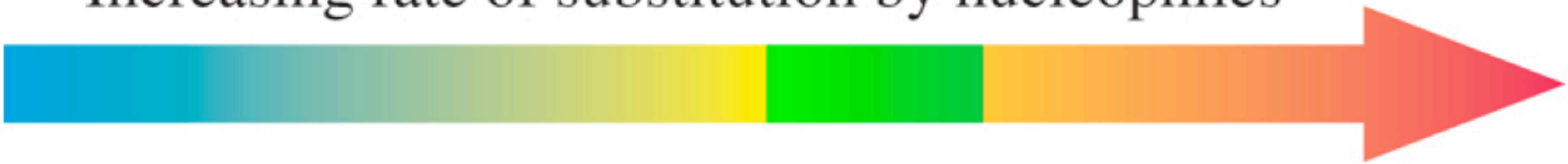
Synthesis: Which starting material could *not* be used to construct the target molecule below?





Reactivity of Halide Leaving Groups

Increasing rate of substitution by nucleophiles



RF << RCl < RBr < RI

Least reactive — Most reactive

HF	HCl	HBr	HBr
pK_a = 3.1	pK_a = -3.9	pK_a = -5.8	pK_a = -10.4

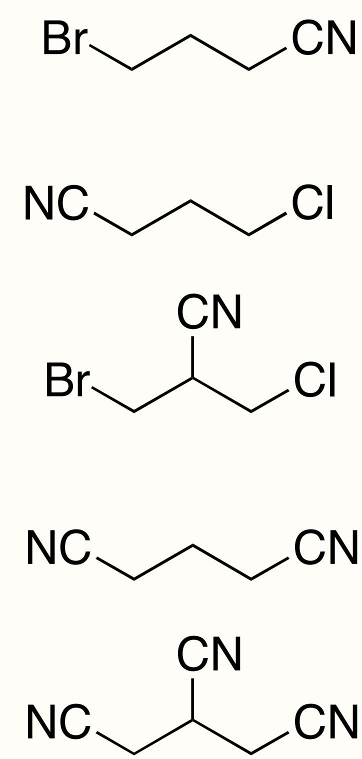
- reactivity of halide leaving groups in nucleophilic substitution is same as for elimination (dehydrohalogenation)
- reactivity related to basicity: weaker base/stronger conjugate acid = better leaving group (most stable conjugate base)

Self-Test Question

A single organic product was obtained when 1-bromo-3-chloropropane was allowed to react with one molar equivalent of sodium cyanide in aqueous ethanol. What was this product?

Br$^-$ is a better leaving group (more reactive) than Cl$^-$

A
B
C
D
E



S_N1 Mechanism of Nucleophilic Substitution

Sections: 8.2-8.5

Review: S_N2 of Alcohols

hydroxyl group　　　halide

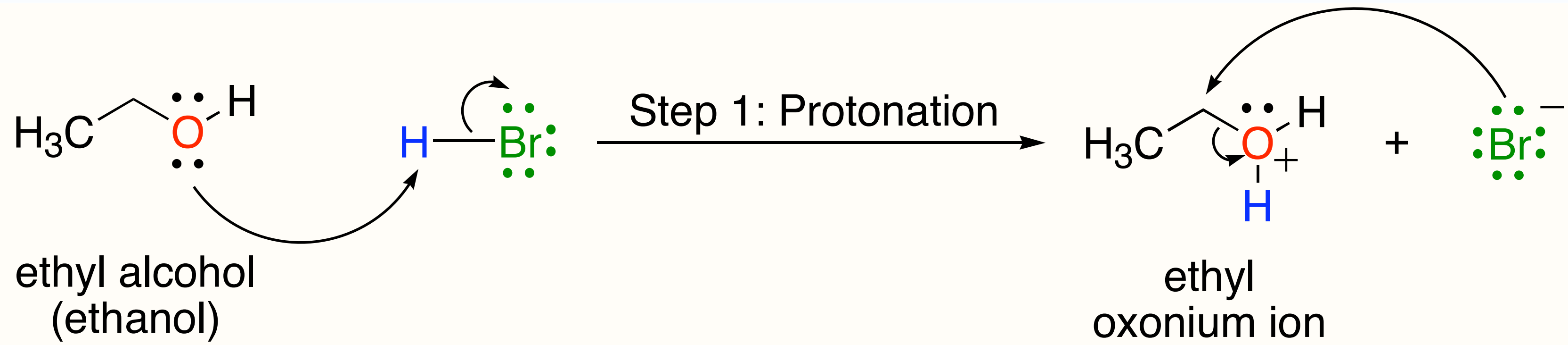
$$\text{R–O–H} + \text{H–X} \longrightarrow \text{R–X} + \text{H–O–H}$$

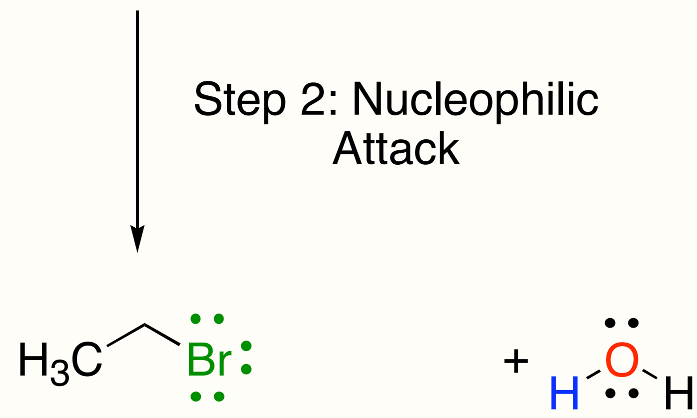
alcohol　　hydrogen halide　　alkyl halide　　water

Hydroxyl group is being <u>substituted</u> (replaced with) a halide

Review: S_N2 of Alcohols

methyl and primary carbocations are too high in energy to be intermediates in nucleophilic substitution reactions





- C-O bond breaks at the **same time** the nucleophile (Br) forms the C-X bond
- RDS is nucleophilic attack; bimolecular, therefore Ingold notation = $\mathbf{S_N2}$
- fewer steps does not mean faster reaction
- rate=k[oxonium ion][halide]

Leaving Groups: Oxonium Ion vs. Halide

R–F > $R–OH_2^+$ >> R–Cl > R–Br > R–I

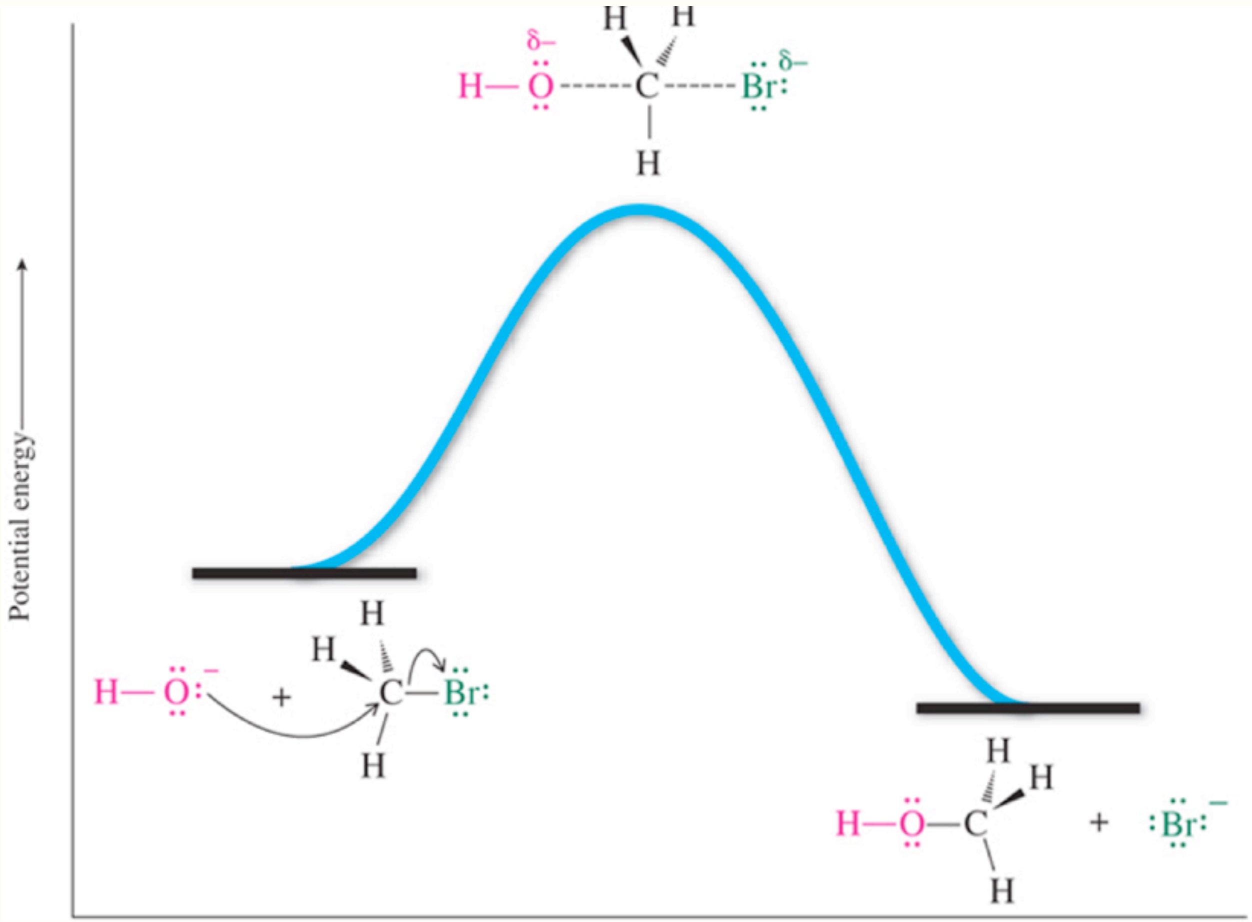
$F^–$ > H_2O >> $Cl^–$ > $Br^–$ > $I^–$

Increasing Leaving Group Ability (Increasing conjugate base stability)

HF	H_3O^+	HCl	HBr	HI
pK_a = 3.1	pK_a = -1.7	pK_a = -3.9	pK_a = -5.8	pK_a = -10.4

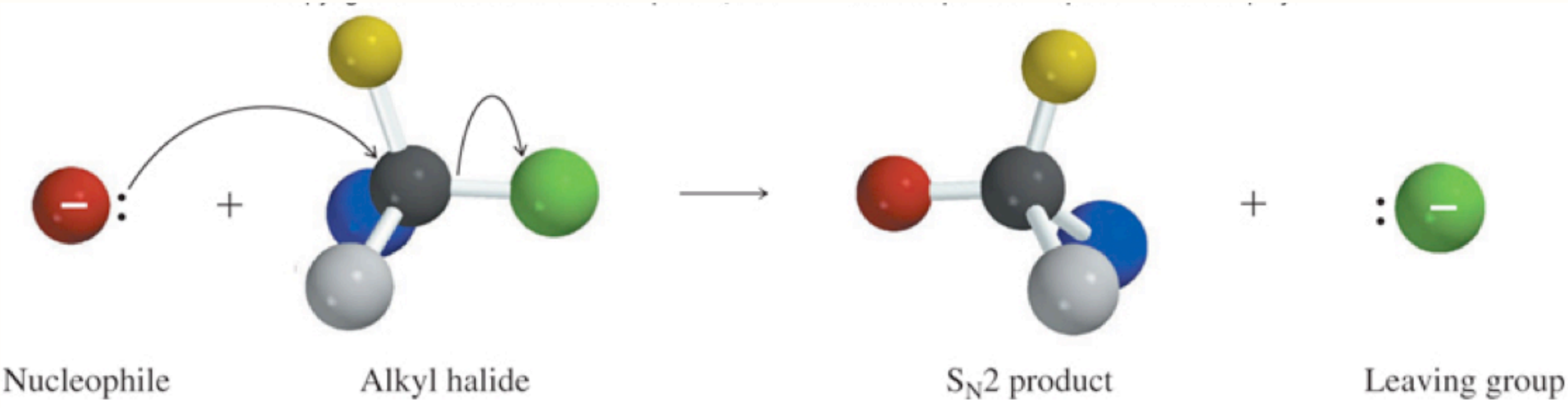
- reactivity of halide leaving groups in nucleophilic substitution is same as for elimination (dehydrohalogenation)
- reactivity related to basicity: weaker base/stronger conjugate acid = better leaving group (most stable conjugate base)

SN2 Mechanism Potential Energy Diagram



- concerted (no intermediates)
- Nuc–C bond forming at the same time as C–LG bond breaking
- no charge development on electrophilic carbon atom
- RDS = bimolecular
- rate=*k*[Nuc][Alkyl Halide]

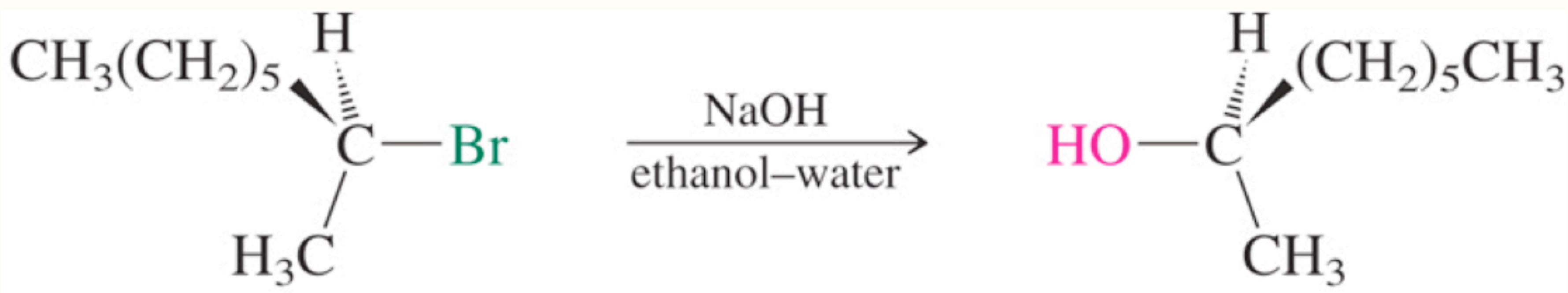
Stereochemistry of S_N2



backside attack: nucleophile forms new bond from the side opposite the bond to the leaving group

Stereochemistry of S_N2

inversion of configuration: the tetrahedral carbon undergoing S_N2 is inverted



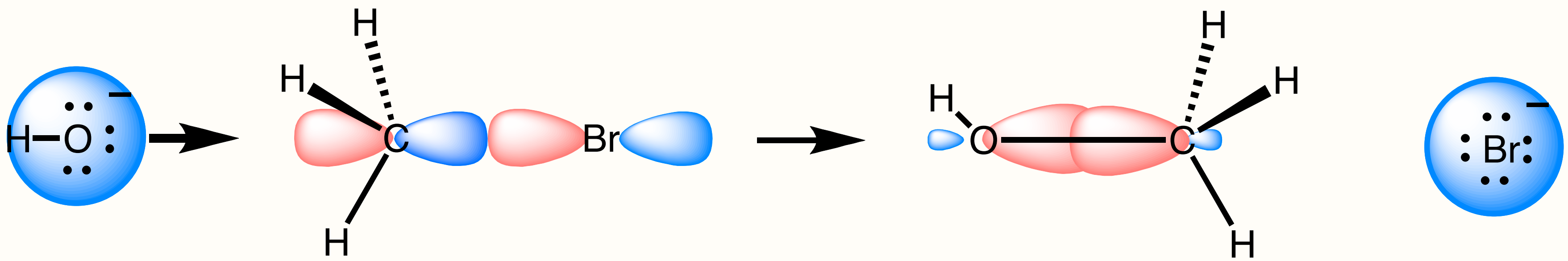
(*S*)-(+)-2-Bromooctane

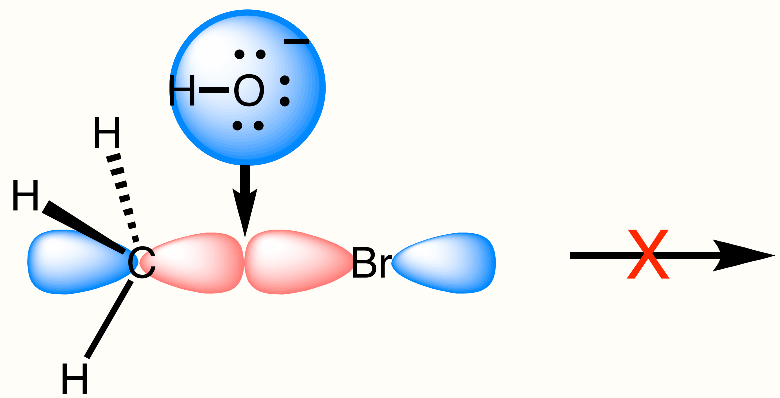
(*R*)-(−)-2-Octanol

Why? We must consider the orbitals forming the bonds in the nucleophile and the electrophile

Stereochemistry of S_N2

Stereoelectronic requirement for nucleophile to overlap with lobe of antibonding molecular orbital that is opposite to halogen

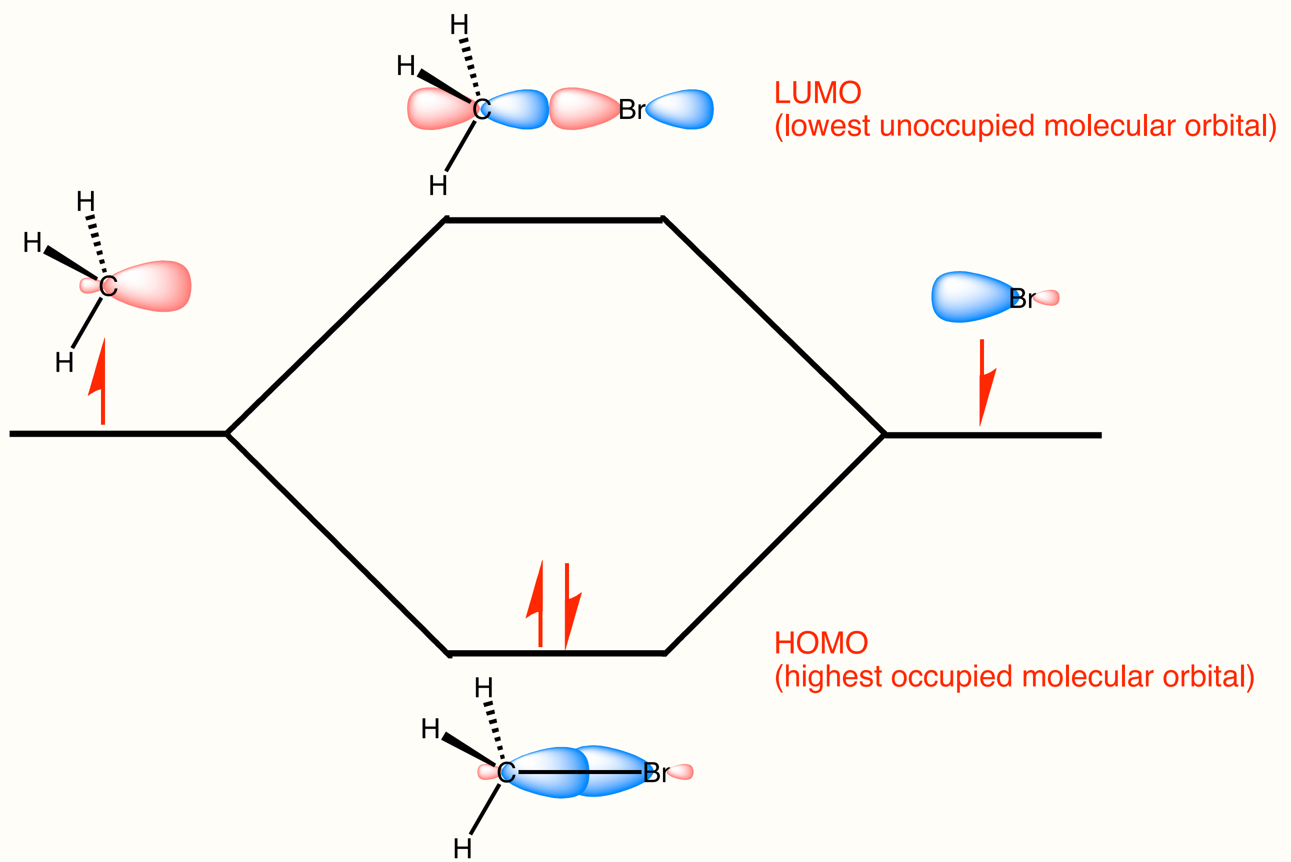




overlap on the same side would involve an equal amount of constructive and destructive interference = no overall bonding

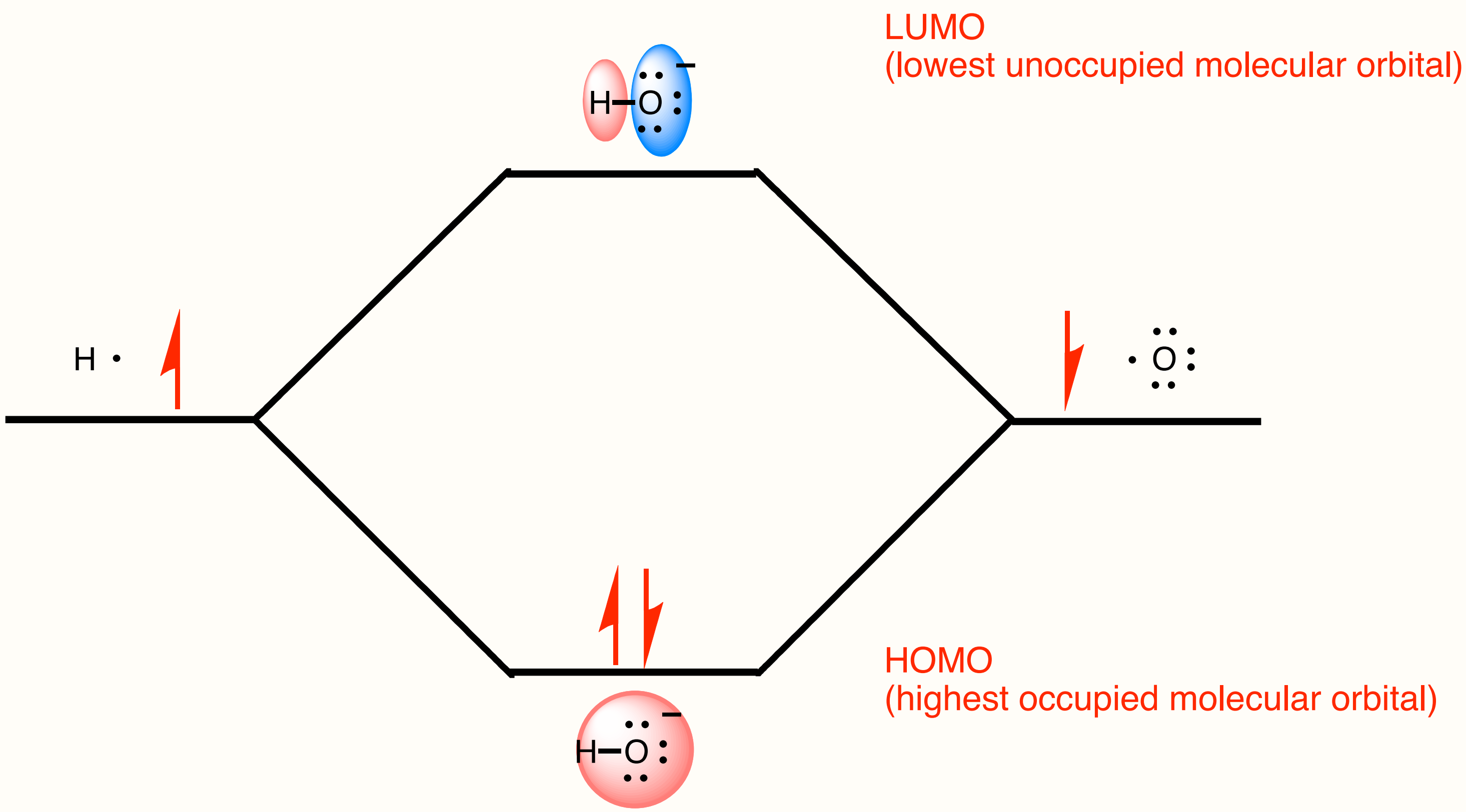
Stereochemistry of S_N2

Generalization: New bonds are formed by overlap between LUMO of electrophile and HOMO of nucleophile



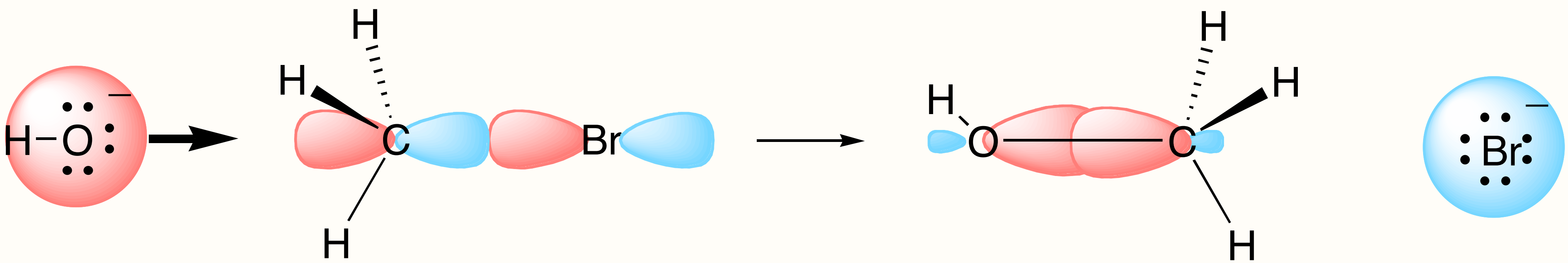
Stereochemistry of S_N2

Generalization: New bonds are formed by overlap between LUMO of electrophile and HOMO of nucleophile



Stereochemistry of S_N2

Electrons in HOMO of nucleophile flow into the empty LUMO of the electrophile



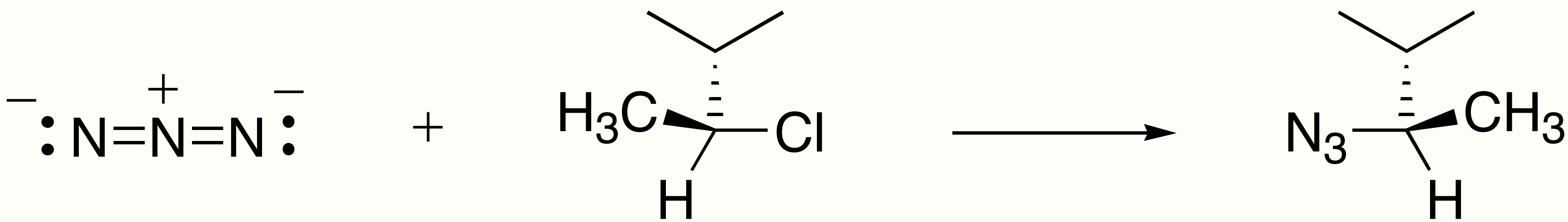
Nucleophile (HOMO)

electrophile (LUMO)

- since the LUMO is an antibonding orbital (σ*), adding electrons to this orbital weakens the C–Br bond until it breaks
- bonding overlap (constructive interference) of HOMO must be from side opposite to C–Br bond to form C–O bond

S_N2 Can Be Stereospecific

Stereospecific - a reaction in which stereoisomeric reactants give stereoisomeric products



Stereospecific S$_N$2

1. Are ≥2 configurational stereoisomers of the reactant <u>possible</u>?

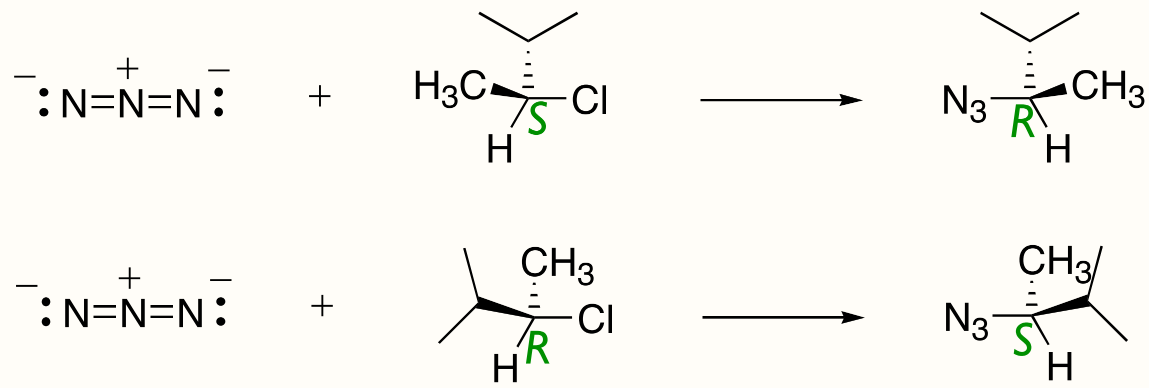
no = can't be stereospecific

yes = go to next question √

2. Are the <u>possible</u> products configurational stereoisomers ?

no = can't be stereospecific

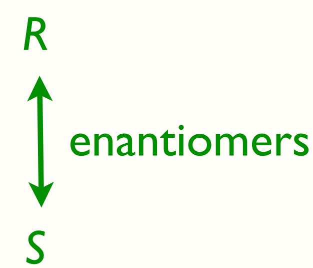
yes = go to next question √



3. Are the products of each configurational reactant stereoisomers of each other ?

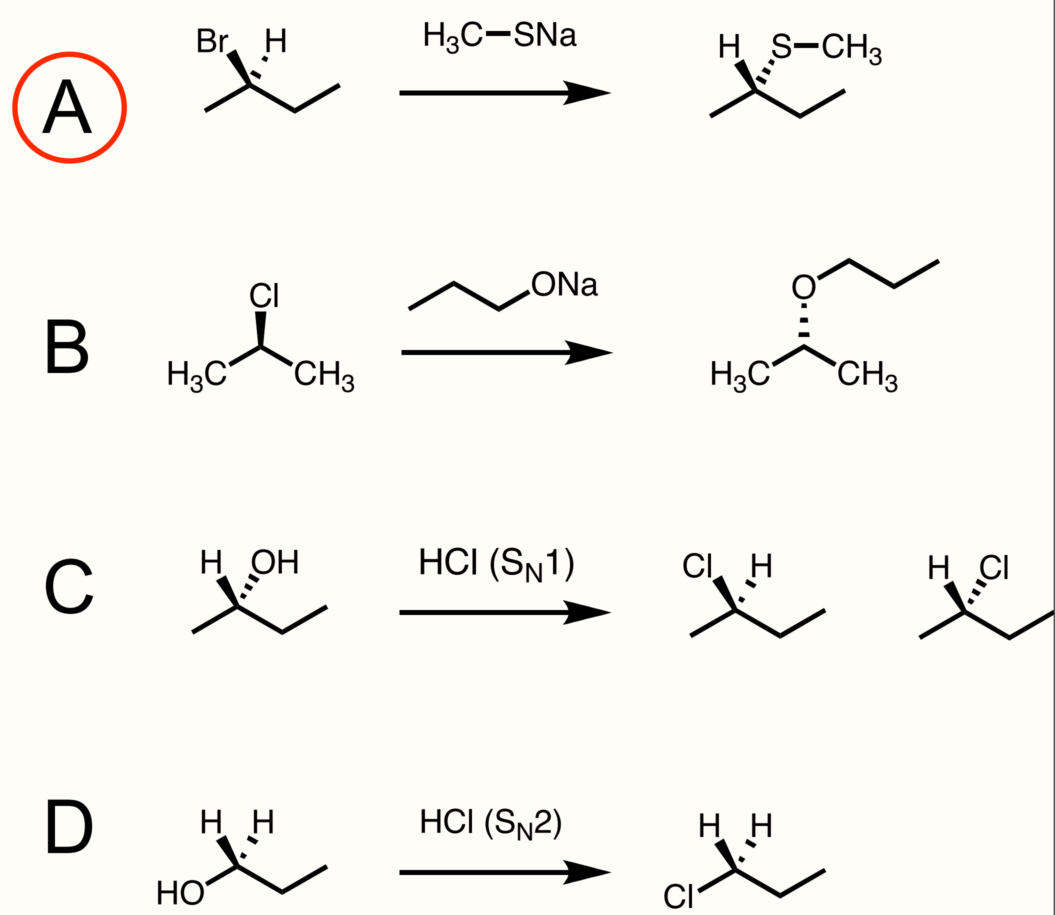
no = can't be stereospecific

yes = go to next question √



Self-Test Question

Which S_N2 reaction below is stereospecific?

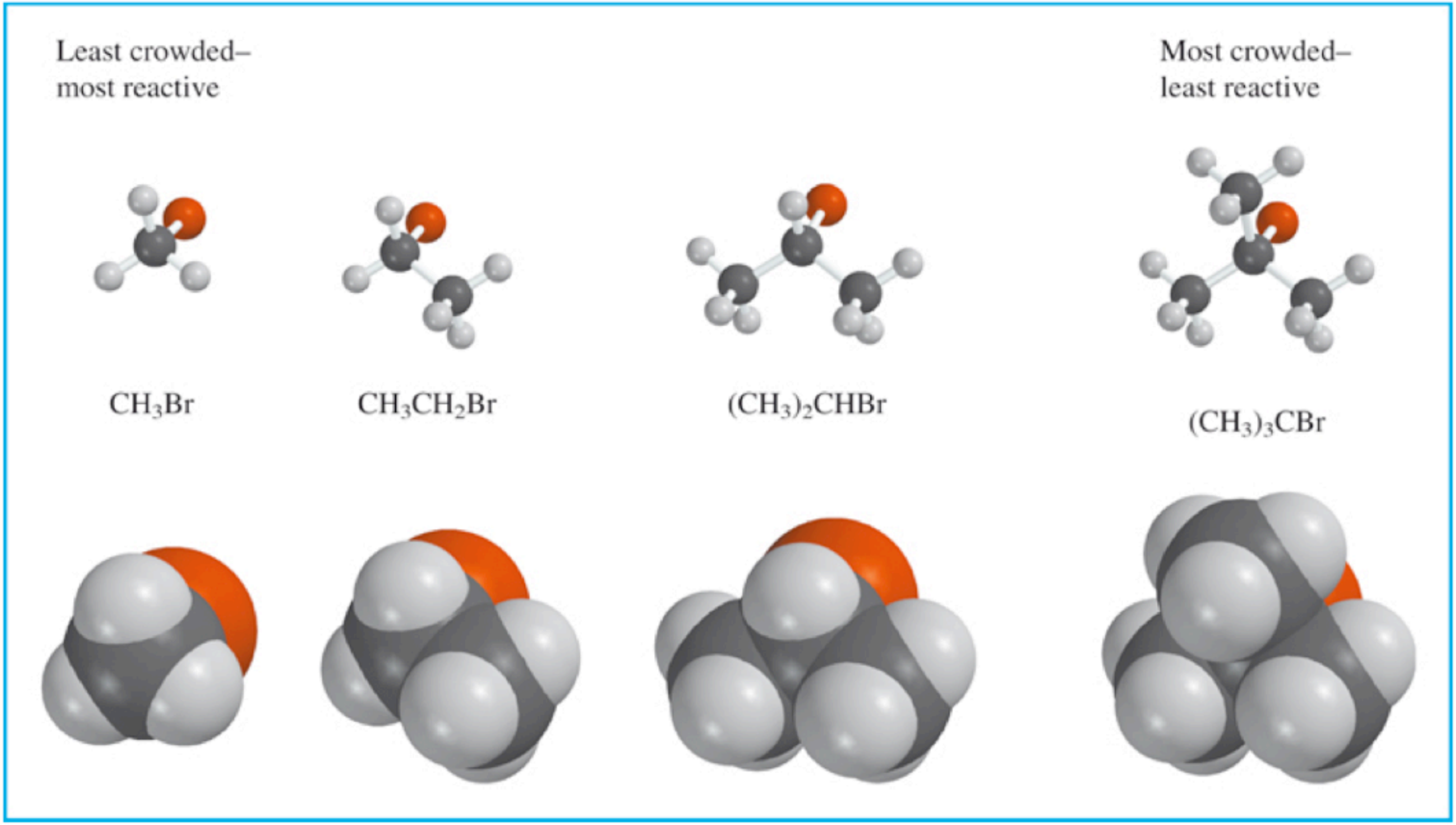


Steric Effects on Rate

Increasing rate of substitution by the S_N2 mechanism

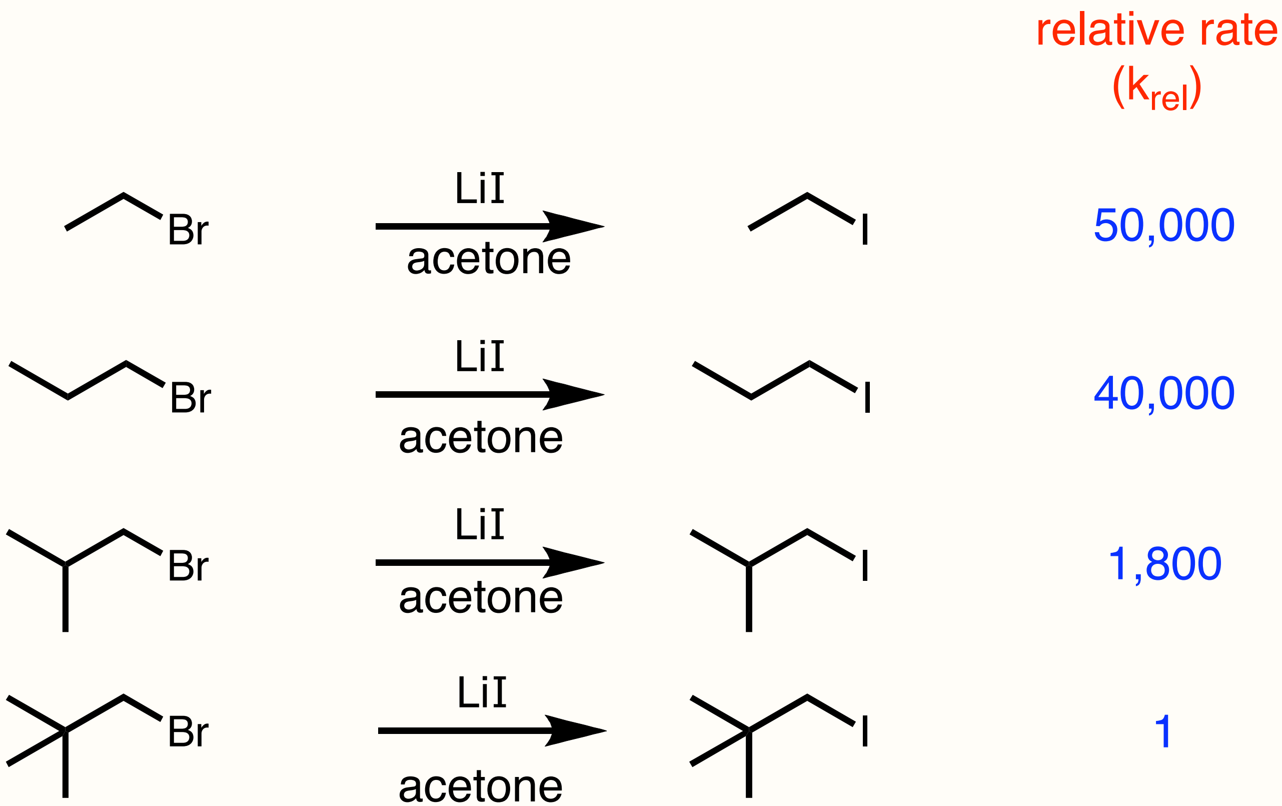
R_3CX	<	R_2CHX	<	RCH_2X	<	CH_3X
Tertiary		Secondary		Primary		Methyl
Least reactive, most crowded						Most reactive, least crowded

Steric Effects on Rate



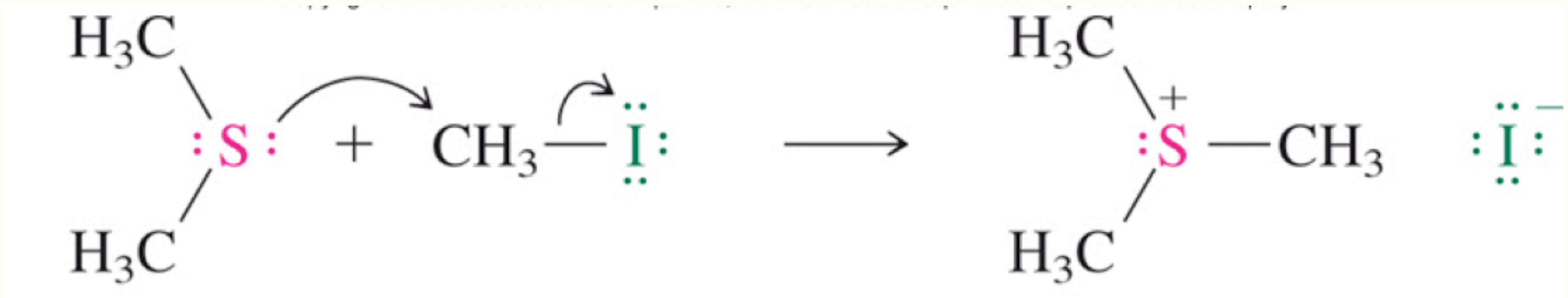
Steric Effects on Rate

steric hinderance *adjacent* to carbon undergoing nucleophilic substitution also decreases rate



Nucleophilicity

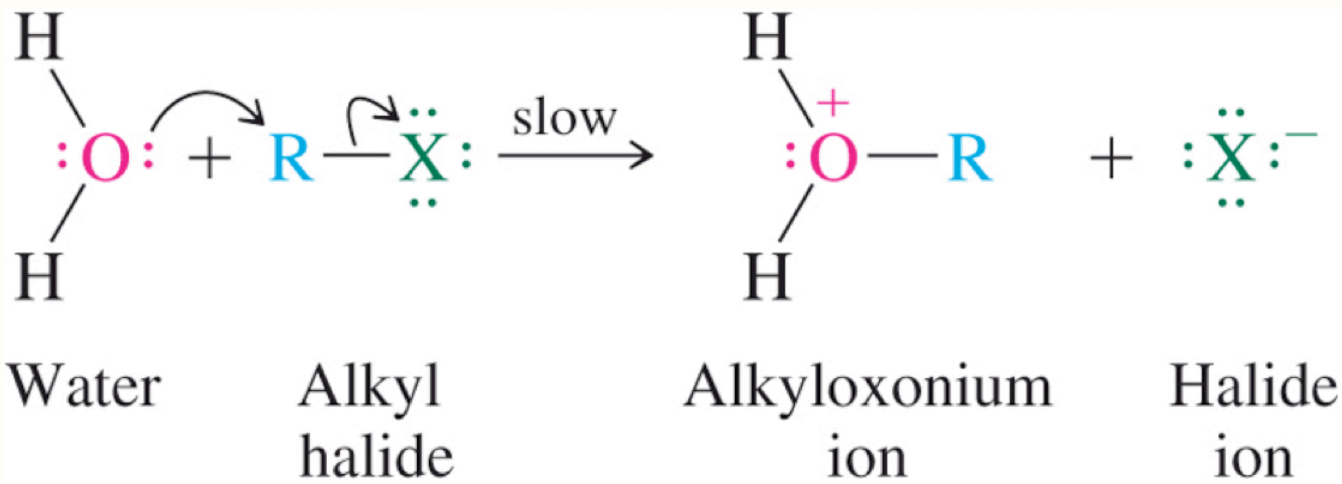
Neutral Lewis Bases may also be nucleophiles

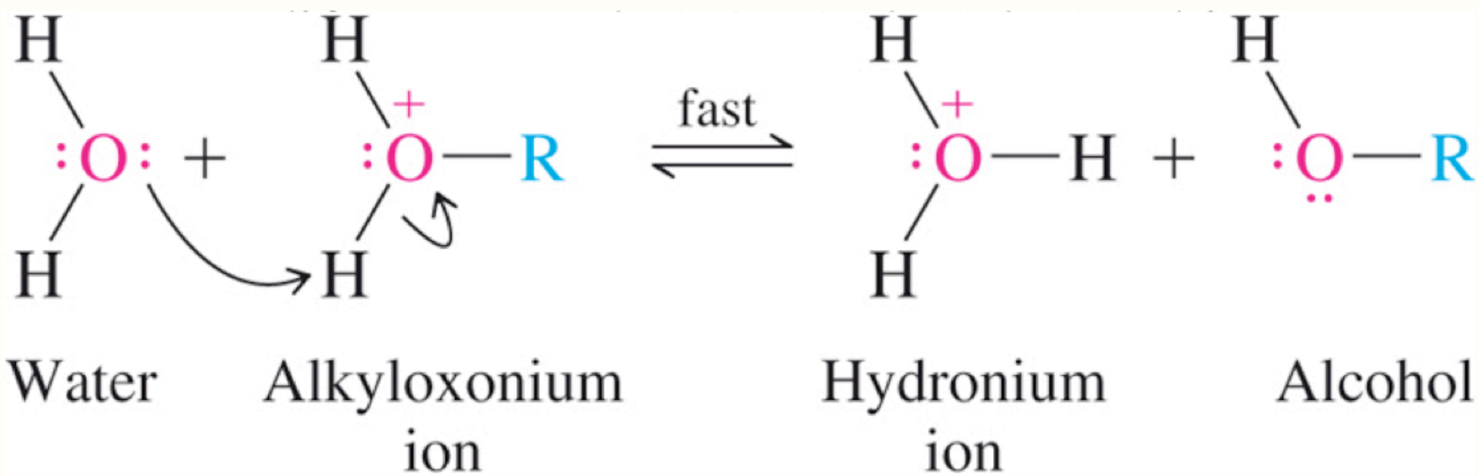


Dimethyl sulfide Methyl iodide Trimethylsulfonium iodide

Nucleophilicity

Neutral Lewis Bases may also be nucleophiles





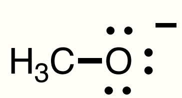
Nucleophilicity

nucleophilicity: measures the strength of the nucleophile ; more nucleophilic = faster SN2 reaction

TABLE 8.4 Nucleophilicity of Some Common Nucleophiles

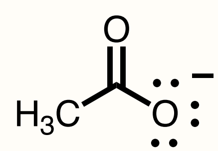
Reactivity class	Nucleophile	Relative reactivity*
Very good nucleophiles	I^-, HS^-, RS^-	$>10^5$
Good nucleophiles	Br^-, HO^-, RO^-, CN^-, N_3^-	10^4
Fair nucleophiles	NH_3, Cl^-, F^-, RCO_2^-	10^3
Weak nucleophiles	H_2O, ROH	1
Very weak nucleophiles	RCO_2H	10^{-2}

1. for identical atoms, more basic = more nucleophilic



CH_3OH
(conjugate acid)
pKa = 15.2

is more nucleophilic than
(stronger base = stronger nuc)



CH_3CO_2H
(conjugate acid)
pKa = 4.7

Nucleophilicity

nucleophilicity: measures the strength of the nucleophile ; more nucleophilic = faster SN2 reaction

TABLE 8.4 Nucleophilicity of Some Common Nucleophiles

Reactivity class	Nucleophile	Relative reactivity*
Very good nucleophiles	I^-, HS^-, RS^-	$>10^5$
Good nucleophiles	Br^-, HO^-, RO^-, CN^-, N_3^-	10^4
Fair nucleophiles	NH_3, Cl^-, F^-, RCO_2^-	10^3
Weak nucleophiles	H_2O, ROH	1
Very weak nucleophiles	RCO_2H	10^{-2}

2. For atoms in the same row and with same charge, nucleophilicity decreases left to right

$H_3C-\ddot{N}H_2$ is more nucleophilic than (stronger base = stronger nuc) $H_3C-\ddot{O}H$

$CH_3NH_3^+$ (conjugate acid)	$CH_3OH_2^+$ (conjugate acid)
pKa = 10.7	pKa = -2

Nucleophilicity

nucleophilicity: measures the strength of the nucleophile ;
more nucleophilic = faster SN2 reaction

TABLE 8.4 Nucleophilicity of Some Common Nucleophiles

Reactivity class	Nucleophile	Relative reactivity*
Very good nucleophiles	I^-, HS^-, RS^-	$>10^5$
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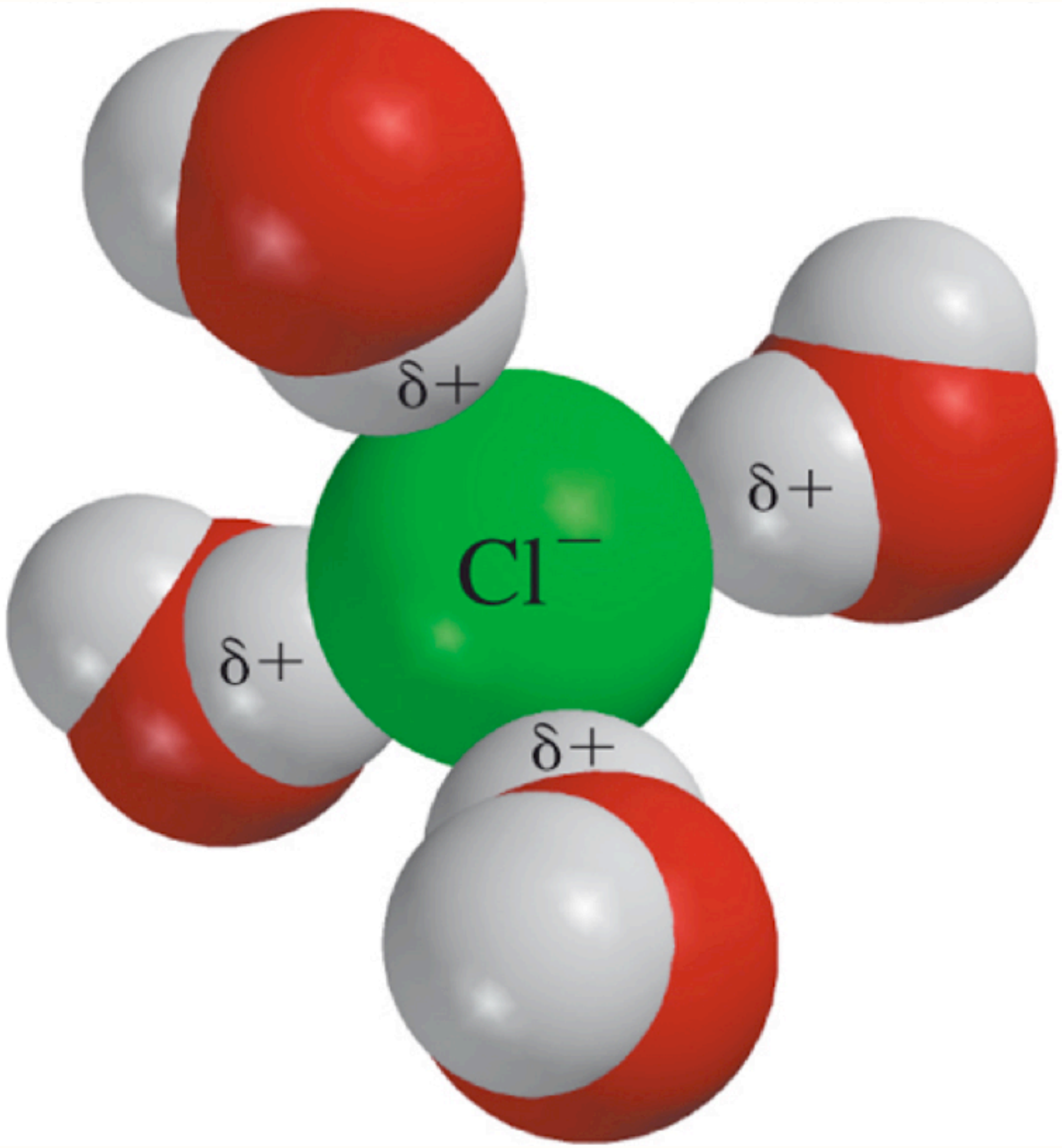
Weak nucleophiles	H_2O, ROH	1
Very weak nucleophiles	RCO_2H	10^{-2}

3. Nucleophilicity does not follow basicity down a column; nucleophilicity increase down a column

$H_3C{-}SH$ is more nucleophilic than $H_3C{-}OH$

I^- is more nucleophilic than Br^-

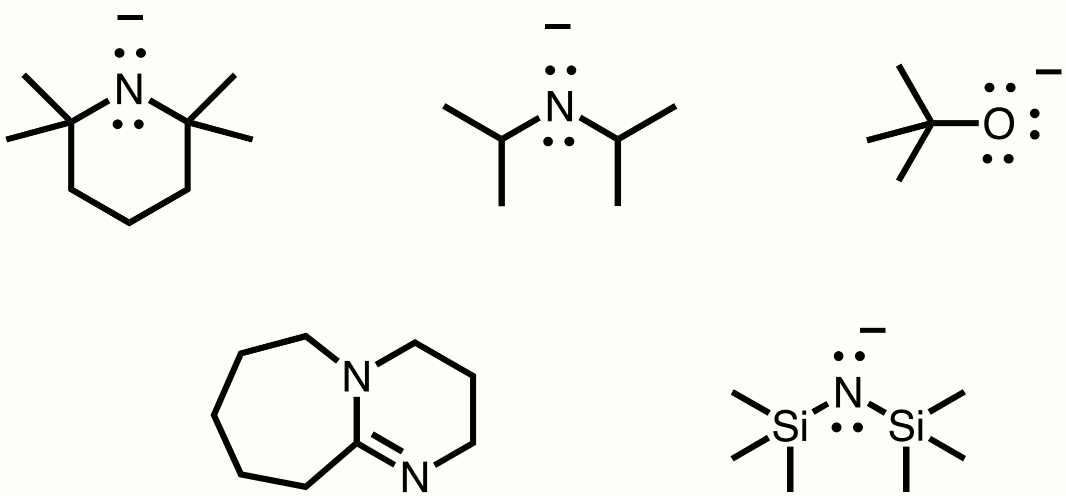
Explanation for Halide Nucleophilicity



- small anions =
- high charge to size ratio =
- ion-dipole forces between halide and solvent strongest for F^- and weakest for I^- =
- F– more solvated
- more difficult for F– to shed solvent molecules to react with electrophile =
- weaker nucleophile

Self-Test Question

All of the molecules/anions below are strong bases. However, each is non-nucleophilic; they do not participate in S_N2 reactions. Why?



A. large van der Waals radius

B. unstable; decompose rapidly

C. each atom already satisfies octet rule; can't form more bonds

D. nucleophiles must be neutral

E. too highly solvated

sterically hindered = non-nucleophilic

Next Lecture. . .

Chapter 8: Sections 8.6-8.13

Quiz This Week. . .

Chapter 7